UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case PGR2025-00085

U.S.Patent 12,168,036

****

ALVOTECH USA INC. and ALVOTECH HF,

Petitioner

vs.

REGENERON PHARMACEUTICALS, INC.,

Patent Owner

****

VIDEOTAPED DEPOSITION OF:

BERNHARDT L. TROUT, PH.D.

DECHERT LLP

One International Place

Boston, Massachusetts

August 27, 2026 8:10 a.m.

Darlene M. Coppola, RPR, RMR, CRR

ALVOTECH 1081
Alvotech v. Regeneron
PGR2025-00085

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EXAMINATION

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BERNHARDT L. TROUT, PH.D

Direct By Mr. Kane 7

EXHIBITS

*(None offered)

P R O C E E D I N G

(Commencing at 8:10 a.m.)

THE VIDEOGRAPHER: Good morning. Here begins Media Unit No. 1 in the videotaped deposition of Bernardt L. Trout, Ph.D., In the Matter of Alvotech USA Inc., et al. versus Regeneron Pharmaceuticals Inc., being filed in the United States Patent and Trademark Office before the Patent Trial and Appeal Board, Case number PGR 202500085.

Today's date is August 27, 2026. The time on the video monitor is 8:11 a.m. The videographer today is Craig Fear representing Planet Depos.

This video deposition is taking place at the Law Offices of Dechert LLP at One International Place in Boston, Massachusetts.

Would all counsel please voice and identify themselves and state whom they represent, beginning with the taking attorney.

MR. KANE: Michael Kane from Fish & Richardson representing Petitioners. 08:11:15 08:11:16

MR. CHEN: Philip Chen from Fish & Richardson representing Petitioners. 08:11:20 08:11:23

MS. KAYALI: Katherine Kayali on behalf of patent owner Regeneron and the witness. With me today are David Burl and Adam Pan. We're all of Williams & Connolly, and also with us is Andrew Gesior of Regeneron. 08:11:25 08:11:25 08:11:29 08:11:32 08:11:35 08:11:37

THE VIDEOGRAPHER: The court reporter today is Darlene Coppola, also representing Planet Depos. 08:11:38 08:11:39 08:11:41

Will the court reporter please swear in the witness, after which counsel may proceed. 08:11:42 08:11:43 08:11:45

// 08:11:54 08:11:54 08:11:54 08:11:54 08:11:54 08:11:54

BERNHARDT L. TROUT, PH.D., 08:11:54
a witness called for examination by 08:11:54
counsel for the Petitioners, having been 08:11:54
satisfactorily identified by the production of 08:11:54
his driver's license and being first duly 08:11:54
sworn by the Notary Public, was examined and 08:11:54
testified as follows: 08:11:54
08:11:54
THE STENOGRAPHER: Thank you. 08:11:55
You may proceed. 08:11:56
08:11:57
DIRECT EXAMINATION 08:11:57
BY MR. KANE: 08:11:58
Q. Good morning, Dr. Trout. 08:11:58
A. Good morning. I think Mr. Kane, if I 08:12:01
heard it correctly. 08:12:02
Q. Kane, yes, Michael Kane. 08:12:03
Can you state your full name for the 08:12:06
record. 08:12:08
A. Yes. It's Bernardt Levy Trout. Levy 08:12:09
has a Y at the end. 08:12:15
Q. And where are you currently employed? 08:12:17

A. I'm currently employed at MIT, Massachusetts Institute of Technology. 08:12:21 08:12:25

Q. And what's your current position? 08:12:29

A. I'm a professor of chemical engineering. 08:12:33 08:12:36

Q. You've been deposed before previously, right? Have you been deposed? 08:12:40 08:12:43

A. Yes. 08:12:46

Q. How many times approximately? 08:12:47

A. I would say probably 25 times or so over about that many years. It may be a little bit more than that. I'm guessing under 30, but... 08:12:51 08:13:00 08:13:02 08:13:05

Q. So you know the -- for the logistics of all of this, I'm going to be asking questions. We have a court reporter taking things down. So it's important that we not talk over each other. We'll try to take a break roughly hourly or so. Okay. 08:13:07 08:13:11 08:13:13 08:13:14 08:13:16 08:13:19

Do you understand that? 08:13:24

A. Yes. 08:13:26

Q. And I'll do my best to ask hopefully 08:13:32

clear questions. If you don't understand anything, please ask me to clarify, and I'm happy to do so. If you don't ask me to clarify, I'm going to assume that you understand my questions. 08:13:35 08:13:37 08:13:41 08:13:43 08:13:44

Is that fair? 08:13:45

A. Yes. I will -- I'll try to clarify if I assume you're asking something that you're not, I'll try to clarify that after, if I can. I'll do my best to make sure I understand. 08:13:50 08:13:53 08:13:57 08:14:01

Q. And there's no reason, for instance, a medical reason or anything along those lines, that would prevent you from giving complete, truthful, and accurate testimony today? 08:14:06 08:14:08 08:14:11 08:14:13

A. No. 08:14:18

Q. So we'll hand you -- 08:14:29

MR. KANE: I'm going to hand you a copy. 08:14:30 08:14:31

MS. KAYALI: Thank you. 08:14:38

BY MR. KANE: 08:14:40

Q. Dr. Trout, I'm handing you a copy of the declaration -- 08:14:40 08:14:42

A. Thank you. 08:14:42
Q. -- that I believe you filed in this 08:14:45
matter. 08:14:47
A. (Witness reviews document.) 08:14:48
MS. KAYALI: Counsel, this does 08:15:01
not have an exhibit number. I'm just assuming 08:15:01
this is Exhibit 2051 in the current 08:15:04
proceeding. 08:15:10
MR. CHEN: Yes, that's right. 08:15:12
BY MR. KANE: 08:15:23
Q. And if you turn to page 273 -- it's 08:15:23
actually not numbered. It's after 272. I 08:15:25
would just ask you to confirm that that's your 08:15:31
signature. 08:15:33
A. (Witness reviews document.) 08:15:34
Yes. And, Counsel, I did bring a 08:15:48
clean copy of, I think, the same document. 08:15:50
The only reason it might be a little more 08:15:54
convenient is because mine is spiral bound and 08:15:57
it -- this might come apart, but I'll follow 08:16:00
your instructions. 08:16:03
Q. You can feel free to use your copy. 08:16:04

A. Okay. Thank you. 08:16:05

Q. And you executed this document on June 19, 2026? 08:16:09 08:16:11

A. Yes. 08:16:17

Q. What did you do to prepare for the deposition today? 08:16:25 08:16:27

MS. KAYALI: I'll caution the witness not to reveal the content of any attorney-client communications, but you can answer without doing so. 08:16:28 08:16:29 08:16:32 08:16:33

A. Well, I reviewed documents. I should say rereviewed documents, including my declaration here, a lot of documents cited, and I, well, thought about it, of course, and I've met with counsel. 08:16:37 08:16:44 08:16:49 08:16:58 08:17:05

// 08:17:12

BY MR. KANE: 08:17:12

Q. When did you meet with counsel? 08:17:12

A. I met -- well, we met, I should say, yesterday and the day before yesterday. 08:17:16 08:17:21

Q. And were those in-person meetings? 08:17:28

A. Yes. 08:17:30

Q. Did you have any Zoom meetings or other calls before that with respect to the deposition? 08:17:32 08:17:34 08:17:38

A. No. 08:17:43

Q. And it was just counsel at the meetings in the previous two days? 08:17:47 08:17:50

A. Yes, only attorneys. 08:17:56

Q. Did you talk to anyone else, other than an attorney, in preparation for your deposition today? 08:17:59 08:18:01 08:18:05

A. No. 08:18:09

Q. Approximately how many hours did you meet with the attorneys? 08:18:13 08:18:14

A. I would say around 14 over two days; kind of a partial day, not quite a full day on Tuesday, and maybe more or less a full day, you know, a 9-to-5 day yesterday. 08:18:21 08:18:29 08:18:36 08:18:40

Q. Did you speak with Dr. Bressler in preparation for the deposition? 08:18:43 08:18:47

A. Oh, no, if you -- like, in the past couple of weeks or specifically in preparation for this deposition, no. 08:18:51 08:18:54 08:18:58

1	Q. So have you spoken with Dr. Bressler	08:19:01
2	since you submitted your declaration in the	08:19:03
3	matter?	08:19:05
4	A. No.	08:19:17
5	Q. How much time did you spend preparing	08:19:19
6	your declaration?	08:19:21
7	A. So before June 19, I think, you're	08:19:30
8	asking me?	08:19:32
9	Q. Yes.	08:19:33
10	A. Yes. As a rough estimate, you know,	08:19:34
11	it's a couple of months ago and before that,	08:19:46
12	but, of course, there's a lot of things going	08:19:49
13	on, and so I would say roughly between 50 and	08:19:51
14	100 hours, maybe somewhere in the middle of	08:19:59
15	that, a rough estimate.	08:20:01
16	Q. And did you draft the declaration	08:20:05
17	yourself?	08:20:07
18	A. I drafted the declaration together	08:20:09
19	with counsel.	08:20:15
20	Q. Did you do any actual drafting or did	08:20:22
21	you just review drafts and edit drafts in	08:20:24
22	conjunction with counsel?	08:20:27

MS. KAYALI: Objection. Vague. 08:20:28

And you're welcome to answer to the 08:20:29

extent you can do so without revealing the 08:20:31

content of any attorney-client communications. 08:20:34

A. I mean, we both contributed. I 08:20:42

certainly typed, if that's what you mean, 08:20:44

significant parts myself, reviewed significant 08:20:51

parts, and it was kind of a back and forth 08:20:53

over some period of time. 08:20:57

BY MR. KANE: 08:21:08

Q. Can you turn to Appendix B in the 08:21:08

declaration. 08:21:13

A. Okay. 08:21:22

Q. And that's entitled, "Materials Relied 08:21:23

Upon." 08:21:26

Do you see that? 08:21:33

A. Yes. 08:21:33

Q. Is this a complete list of materials 08:21:36

that you relied upon in forming your opinions 08:21:39

set forth in the declaration? 08:21:42

A. (Witness reviews document.) 08:21:48

My intention is to make it -- or was 08:22:14

to make it complete. If there's anything I referenced in here that didn't make it, I would say I relied on those too. I don't -- I don't think so. I think it was complete. At least that was certainly my intention. Hopefully it, indeed, is. 08:22:17 08:22:22 08:22:25 08:22:29 08:22:32 08:22:34

Q. And you said in preparation for your deposition, you had reviewed this declaration again recently? 08:22:46 08:22:48 08:22:50

A. Yes. 08:22:54

Q. Is there anything in the declaration that you spotted, typos or otherwise, that you would like to correct? 08:22:56 08:22:57 08:23:01

A. I did spot some typos. I don't have it memorized where they are. I think they were pretty evident. 08:23:06 08:23:12 08:23:15

And then I did find one place, again, if we get to it, I can specifically point it out. I think I -- I guess it's kind of a typo, but I just did a ratio calculation, and I remember it was a calculation of an excipient. I had put one-third. When I 08:23:21 08:23:25 08:23:27 08:23:32 08:23:37 08:23:41

1	double-checked it, I think, yesterday, it's	08:23:46
2	probably one-fourth. I don't think that	08:23:48
3	difference is substantive. I can try to find	08:23:50
4	it, if you want me to. But basically, I think	08:23:52
5	there were some typos. That's the only thing	08:23:57
6	there could be, you know, slightly	08:24:00
7	substantive, but it didn't affect my opinions	08:24:01
8	at all.	08:24:04
9	Q. And we'll see if we can get to the	08:24:04
10	ratio. We can figure that out later. We	08:24:12
11	don't need to look for right now, but thank	08:24:14
12	you for that.	08:24:16
13	A. Mr. Kane, there is a fan blowing. If	08:24:17
14	you don't mind speaking up a little bit just I	08:24:19
15	would appreciate it. I could hear you but...	08:24:22
16	Q. I will try to speak louder.	08:24:26
17	A. Thank you.	08:24:27
18	Q. And I wanted to look at your CV for a	08:24:34
19	minute, Dr. Trout, which is Appendix A in your	08:24:38
20	declaration.	08:24:42
21	A. Okay. I am there.	08:25:08
22	Q. I notice under your research	08:25:10

interests, you identify "pharmaceutical manufacturing and development research." 08:25:11 08:25:13

Do you see that? 08:25:22

A. Yes. 08:25:22

Q. Can you give me a high-level summary of what your research in pharmaceutical manufacturing has entailed? 08:25:23 08:25:28 08:25:31

A. Of course. I'll touch upon the development because it's related, but I'll focus on the manufacturing. That's why they're together. 08:25:41 08:25:46 08:25:50 08:25:54

So my focus on manufacturing has been technologies to make pharmaceutical processing more efficient, a whole variety of, I'd say, methodologies, including continuous manufacturing and then developed equipment in our laboratory, new equipment. And the reason why that's very high level, of course, I can go into more detail as you wish; but it's also related to the development research. The idea being that development, meaning product development. We've been aiming to have a 08:25:56 08:26:01 08:26:06 08:26:14 08:26:17 08:26:26 08:26:31 08:26:35 08:26:39 08:26:43 08:26:49

mutual influence in the manufacturing process development and the product development, so they're not completely independent, and that is related to the biopharmaceutical in the next -- in, I guess, the next item on the research list. 08:26:55 08:26:59 08:27:02 08:27:05 08:27:09 08:27:14

Q. Right. And so yes, can you describe for me again the biopharmaceutical, and it says "(protein and antibody) processes and stabilization." 08:27:16 08:27:19 08:27:22 08:27:29

Can you describe the work in that area? 08:27:31 08:27:32

A. Yes. I've been working in that area for over two decades getting -- well, if -- that's only counting my work at MIT. I actually started working on bioprocessing as an undergraduate. 08:27:35 08:27:39 08:27:46 08:27:49 08:27:53

Apologies. I should clarify. 08:27:54

Almost three decades is my work as an independent researcher professor at MIT. I did work when I was a student at MIT starting as an undergraduate, and the work is sort of a 08:27:57 08:28:00 08:28:05 08:28:08

subset of the broader work that I mentioned focusing on biopharmaceuticals, so proteins broadly. For several years there was a particular focus on antibodies. And the idea there was to advance the field to understand better degradation processes and how to stabilize the proteins in formulations, to hinder those degradation processes, including viscosity, not necessarily degradation per se, but important for biopharmaceutical products, and then connecting that understanding, on the one hand, to discovery. So kind of upstream. And then processing downstream. 08:28:18 08:28:22 08:28:26 08:28:32 08:28:37 08:28:41 08:28:48 08:28:55 08:29:01 08:29:04 08:29:10 08:29:14 08:29:19

That's a very high-level answer. I could go into all detail as you wish. 08:29:23 08:29:25

Q. In that area of work, have you consulted with pharmaceutical companies? 08:29:34 08:29:40

MS. KAYALI: I'll caution the witness not to reveal any third-party confidential information, but you can answer to the extent that you're able to do so without violating any confidentiality 08:29:48 08:29:48 08:29:51 08:29:52 08:29:57

requirements. 08:29:59

A. Yes. 08:30:01

BY MR. KANE: 08:30:05

Q. And have you consulted for Regeneron? 08:30:05

A. In general, I don't talk about the 08:30:16

specifics of the clients. Sometimes there's 08:30:21

confidentiality involved. 08:30:23

Given I think the importance of 08:30:28

Regeneron in particular, I will say that 08:30:30

I've -- outside of this sort of legal 08:30:35

engagement, I have not otherwise consulted 08:30:40

with Regeneron. 08:30:41

BY MR. KANE: 08:30:46

Q. Yes, and I appreciate that. I 08:30:46

understand that you've been involved in other 08:30:47

legal matters for them. 08:30:48

Without giving any specifics of any -- 08:30:56

and I don't want any confidential information, 08:30:58

but have you been involved in developing 08:30:59

processes for biopharmaceuticals that have 08:31:02

reached the market? 08:31:08

MS. KAYALI: And again, please 08:31:11

don't reveal any third-party confidential information, and you can answer without doing so. 08:31:12 08:31:14 08:31:16

THE WITNESS: Okay. 08:31:17

A. Yes, as a consultant. Again, I won't be able to go into details, but just at that high level, yes. 08:31:17 08:31:25 08:31:29

BY MR. KANE: 08:31:32

Q. Okay. If you -- if you look at page 3 of your CV, I see under conference -- conferences and organization -- "Conferences Organization" is the title there at the bottom. 08:31:32 08:31:35 08:31:42 08:31:44 08:31:46

Do you see that? 08:31:47

A. Yes. 08:31:51

Q. And I see several conferences relating to continuous manufacturing. Do you see those? 08:31:53 08:32:08 08:32:10

A. Yes. 08:32:17

Q. So what is continuous manufacturing? 08:32:19

A. And I should also emphasize, these are really the conferences that I was a cochair, a 08:32:23 08:32:27

very high level. I've clearly organized a lot of other sessions and whatnot at various conferences with other people where the chair or cochair. 08:32:33 08:32:36 08:32:40 08:32:44

Q. Sure. 08:32:45

A. So this is those particular -- that particular level. 08:32:46 08:32:49

Well, at a very high level, continuous manufacturing could be considered the next level of quality by design, which was an approach in the industry where now it's over 15 years ago when I start -- maybe it's 20 now, when I started continuous, it was newer than that. 08:33:01 08:33:03 08:33:06 08:33:12 08:33:17 08:33:19 08:33:24

And then ideally continuous manufacturing involves continuous process flow, although often it's not end-to-end, but that's the objective. 08:33:27 08:33:29 08:33:33 08:33:41

It typically involves inline analytics, model -- and model-based control, and a systems engineering approach. 08:33:45 08:33:47 08:33:51

So that would be a very high level. 08:33:53

Q. And I believe I saw in some of the materials that I reviewed that you had done some project with Novartis and potentially received some award in the continuous manufacturing area. I don't believe it was in the CV. It was in a publication that I read. 08:34:01 08:34:06 08:34:09 08:34:12 08:34:14 08:34:22

A. Oh, well, let me clarify. I've -- well, a couple things. 08:34:26 08:34:31

I have -- excuse me. I -- well, I wouldn't quite say I did work for Novartis. I was director of a collaboration through MIT, maybe just a slight technicality, because we don't do work for hire per se, we do research which is intended to be published, educating students. 08:34:40 08:34:44 08:34:48 08:34:53 08:34:57 08:35:01 08:35:04

And actually, under positions, I do have that. I have -- if you're on the first page, kind of the middle section, "Positions." 08:35:11 08:35:12 08:35:15

Q. Yes. 08:35:28

A. Under Massachusetts Institute of Technology, the third line is that I was director of the Novartis MIT Center for 08:35:29 08:35:30 08:35:32

Continuous Manufacturing. 08:35:37

And then in the next page, under 08:35:41

"Awards," I think there's several awards that 08:35:44

I have listed here that are specifically for 08:35:48

the work in continuous manufacturing. 08:35:51

Just to be clear, they weren't from 08:35:55

Novartis, they were from other entities. 08:35:57

Q. Thank you for that clarification. 08:36:03

Was the work on an actual process 08:36:05

inside a Novartis plant, or was it more 08:36:07

general research based? 08:36:10

MS. KAYALI: And again, please 08:36:12

don't reveal any third-party confidential 08:36:12

information in your answer. If you're able to 08:36:15

do so based -- if you're able to answer based 08:36:18

on public information, feel free to do so. 08:36:20

THE WITNESS: Understood. 08:36:26

A. It was a significant collaboration 08:36:30

with Novartis. We did, I'd say, research work 08:36:33

at MIT, including developing a pilot 08:36:38

end-to-end continuous process. 08:36:42

When I say "pilot," it's not GMP 08:36:47

level. It was intended to be a research tool, and certainly we've worked with Novartis. 08:36:51 08:36:54

It's not -- it's public that they've had -- have had and have a continuous manufacturing initiative, so they've installed their own equipment at Novartis. Certainly discussed these things with them and the various interactions over the decade-plus collaboration, if that's what you were getting at. 08:37:00 08:37:02 08:37:06 08:37:08 08:37:18 08:37:21 08:37:25 08:37:28

BY MR. KANE: 08:37:30

Q. Okay. And in this work -- I'm not sure exactly what bucket you would put it into, what kind of parameters are you trying to control in these manufacturing processes? 08:37:30 08:37:35 08:37:36 08:37:44

MS. KAYALI: Objection. Vague. 08:37:53

And again, please don't reveal third-party confidential information. You can answer based on public information. 08:37:54 08:37:56 08:37:57

A. I'm trying to understand. When you say "this work," what are you referring to and -- 08:38:04 08:38:05 08:38:07

BY MR. KANE: 08:38:09
Q. Well -- 08:38:09
A. -- what do you mean by "parameters"? 08:38:10
Q. Sure. I guess I'm just trying to 08:38:11
understand, is this work directed at, for 08:38:14
instance, process control in the sense of 08:38:17
being able to maintain specifications of the 08:38:23
output? 08:38:28
MS. KAYALI: Objection. Vague. 08:38:31
BY MR. KANE: 08:38:34
Q. So, for instance, if you're trying to 08:38:34
manufacture a protein product that the 08:38:35
specification is 40 milligrams per milliliter 08:38:39
plus or minus 10 percent, is that -- is the 08:38:46
work that you were working on directed at 08:38:51
trying to help the processes maintain those 08:38:55
specifications or to tighten control over the 08:38:57
process? 08:39:01
MS. KAYALI: Objection. Vague. 08:39:03
A. Maybe I don't quite understand. I'll 08:39:10
try to answer as best I can. 08:39:13
So in batch -- and I think you're 08:39:19

asking about continuous manufacturing specifically. 08:39:21 08:39:23

I see you're nodding your head, so I think that's correct. 08:39:24 08:39:28

In batch manufacturing, there are individual steps, and generally the product is moved, even manually, could be moved between different plants from step to step. 08:39:30 08:39:35 08:39:39 08:39:47

And in continuous, the objective is to integrate that. And in doing so, that means understanding your process better to integrate. 08:39:53 08:39:56 08:40:03 08:40:05

And then just to clarify, the quality part means, I would say, meeting final specifications. So I think if I understood your use of that word, that's right, it's more having -- being in a state of control of the process during the entire time when product is produced. 08:40:09 08:40:12 08:40:18 08:40:21 08:40:26 08:40:30 08:40:38

And so it doesn't mean -- I wouldn't say necessarily tighter specifications. Again, we're talking very high level. It 08:40:41 08:40:45 08:40:49

means higher level of control to meet the specifications that would be needed, and this would be, you know, a discussion between the company and the FDA or other regulatory agencies, for example. 08:40:52 08:40:58 08:41:05 08:41:09 08:41:12

BY MR. KANE: 08:41:31

Q. And so in that process, you said the company would talk to FDA or whatever appropriate regulatory body to develop specifications in terms of quality control, correct? 08:41:31 08:41:34 08:41:35 08:41:37 08:41:43

MS. KAYALI: Objection. Vague. 08:41:44 08:41:44

A. I think generally, the procedure is that -- I mean, there's -- just at a high level, the company would propose something to the FDA. There would be feedback. There can be some back and forth. There could be meetings. There could also be meetings even before the company proposes to get verbal feedback, and that's the approach at a high level. 08:41:52 08:41:59 08:42:03 08:42:06 08:42:10 08:42:12 08:42:15 08:42:20 08:42:22

BY MR. KANE: 08:42:24
Q. Right. And then -- and once those 08:42:24
specifications are identified, then they go 08:42:25
back to the manufacturing process control 08:42:30
people in order to set a process, in order to 08:42:33
meet the specifications in my understanding; 08:42:36
is that right? 08:42:43
MS. KAYALI: Objection. 08:42:44
Vague. 08:42:50
A. As I -- to the extent I understand 08:42:50
your question, I don't think it's quite such a 08:42:52
step -- simplistic step process like that. 08:42:57
BY MR. KANE: 08:43:03
Q. Okay. And I guess what I'm trying to 08:43:03
get to is, is the work that you've done -- 08:43:08
let's start with the continuous manufacturing 08:43:11
first, been involved in attempting to meet 08:43:12
those quality specifications for the end 08:43:18
product? 08:43:22
MS. KAYALI: Objection. Vague. 08:43:26
A. By those -- I'm not quite sure what 08:43:33
you mean. 08:43:38

BY MR. KANE: 08:43:40
Q. So -- 08:43:40
A. This is not just, like, a linear 08:43:40
process. 08:43:42
Q. I understand. Again, maybe try to 08:43:43
give you a little more what I'm thinking 08:43:45
about. 08:43:48
But, for instance, in my sort of 08:43:50
hypothetical, a protein formulation, antibody 08:43:50
formulation, 40 mgs per mL concentration plus 08:43:53
or minus 10 percent; pH of 5.5, plus or minus, 08:44:02
you know, .5 pH units; viscosity of 20 08:44:06
centipoise plus or minus 10 percent. In my 08:44:16
hypothetical, we have specifications along 08:44:22
those lines. 08:44:24
Is the process -- the continuous 08:44:26
manufacturing process then that you have 08:44:28
worked on and developed trying to create an 08:44:30
end product that meets those specifications? 08:44:35
MS. KAYALI: Objection. 08:44:38
Incomplete hypothetical. Vague. 08:44:39
A. I would say, again, to the extent I 08:44:48

understand your question, of course, companies generally have release specifications, and the process should lead to a product that meets those specifications to be released. 08:44:54 08:44:58 08:45:07 08:45:09

The idea behind continuous manufacturing, as I mentioned, is to develop, let's say, a better technical understanding of the process to understand better what the critical process parameters are that lead to the desired quality attributes; and so to get a tighter understanding, not a tighter specification, but a tighter understanding of the connection between those two. 08:45:14 08:45:17 08:45:23 08:45:27 08:45:31 08:45:38 08:45:42 08:45:46 08:45:49

BY MR. KANE: 08:46:01

Q. And shifting to the batch manufacturing type processes, have you consulted on those type processes as well? 08:46:01 08:46:05 08:46:07

MS. KAYALI: Again, you can answer without revealing third-party confidential information. 08:46:12 08:46:12 08:46:15

A. Yes. 08:46:18

BY MR. KANE: 08:46:23

Q. And similarly, the desired goal for the batch manufacturing process is to have an output of product that meets the desired specifications, correct? 08:46:23 08:46:27 08:46:32 08:46:35

A. Just to make sure, you said "desired goal"? 08:46:42 08:46:44

Q. Yes. 08:46:51

A. Okay. I mean, I guess you could say that at a high level, I think that -- I guess the question is what -- what you mean by "desired specifications." It's not, I think, a term that's defined per se. I mean -- 08:46:52 08:46:57 08:47:01 08:47:04 08:47:12

Q. Well, I understand, but I had given you some examples of what I was thinking about. 08:47:16 08:47:18 08:47:21

But specifically if it was an FDA-approved product, there are certain release specifications. The goal is to have a manufacturing process that can output a product that satisfies the specifications submitted to the FDA as part of the approval process. 08:47:22 08:47:23 08:47:25 08:47:28 08:47:29 08:47:38 08:47:41

MS. KAYALI: Objection. Vague. 08:47:45

A. I would say that if you're asking 08:47:52

about producing product, the goal is to 08:47:54

produce product that meets the specifications 08:48:00

that have been, let's say, agreed upon or 08:48:08

approved by the FDA and other, of course, 08:48:10

regulatory agencies, and to minimize, ideally 08:48:14

not have out-of-spec products. 08:48:23

BY MR. KANE: 08:48:26

Q. Okay. And in your experience, again, 08:48:26

nothing specific, but in your experience in 08:48:32

these types of protein manufacturing 08:48:35

processes, what are the typical tolerances or 08:48:39

ranges for the parameters, maybe starting with 08:48:55

the concentration of the protein? 08:48:59

Is it plus or minus 5 percent? Plus 08:49:02

or minus 10 percent? Plus or minus 15 08:49:05

percent? Do you have any background 08:49:08

experience in that area? 08:49:09

MS. KAYALI: Objection. 08:49:12

Foundation, scope, and vague. 08:49:13

A. I would say yes, I have experience in 08:49:25

that area. And to the extent I understand your question, I will tell you what I've been told many, many times with many interactions with regulatory bodies, international regulatory bodies, regulators, the FDA, including management, which is that they don't set, on a high level, specifications ahead of time. 08:49:29 08:49:34 08:49:38 08:49:42 08:49:48 08:49:52 08:49:57 08:50:01

It's up to the manufacturer to propose their specifications and then justify them. They don't want to peremptorily make some broad rule of specifications. 08:50:04 08:50:07 08:50:13 08:50:18

BY MR. KANE: 08:50:35

Q. Have you seen specifications that have been proposed or put in place by -- in response to the FDA at any of these facilities that you've consulted with? 08:50:35 08:50:39 08:50:44 08:50:47

MS. KAYALI: Again, please don't reveal any particular third party's confidential information. You can answer without doing so. 08:50:49 08:50:50 08:50:53 08:50:54

A. It's your question. I'm not sure if 08:51:02

you wanted to ask it that way. You mean have I seen specifications at a facility? 08:51:05 08:51:06

BY MR. KANE: 08:51:11

Q. Yes. 08:51:11

A. When I was at a facility? 08:51:13

Q. Well, or just you were aware of the specification for a particular manufacturing process. 08:51:17 08:51:18 08:51:20

MS. KAYALI: Again, please don't reveal any particular third-party confidential specifications. If you can answer the question without doing that, feel free. 08:51:23 08:51:24 08:51:29 08:51:31

A. I'm, again, not sure if you meant to ask the question the way you did. 08:51:41 08:51:42

As best I understand, I'm certainly aware, and have been over the years, of specifications that manufacturers have proposed and have, say, the FDA I think was your regulatory body, has approved. 08:51:47 08:51:48 08:51:53 08:51:58 08:52:03

BY MR. KANE: 08:52:09

Q. Okay. And again, starting with, like, protein concentration, what have you -- 08:52:09 08:52:16

without any specifics, but what types of specifications in terms of protein concentration have you seen? 08:52:20 08:52:24 08:52:27

MS. KAYALI: Objection. Vague. 08:52:31

BY MR. KANE: 08:52:31

Q. Or become aware of? 08:52:39

A. Okay. So just to be clear, I think your other example you were asking about, as I understood it, fill volume. Now you're asking about concentration? 08:52:43 08:52:51 08:52:56 08:52:59

Q. Concentration, yes. 08:53:01

A. Okay. Yes, I think there's going to be generally -- again, there can always be exceptions, but I think in general, by concentration I'm presuming you're -- maybe I shouldn't presume. 08:53:03 08:53:08 08:53:14 08:53:19 08:53:22

You mean in a liquid formulation of some sort? 08:53:24 08:53:26

Q. Right. I'm talking about a liquid protein formulation, milligrams per milliliter, typical units. 08:53:27 08:53:29 08:53:32

A. I think that there is generally a 08:53:36

specification as to concentration in, let's say, documents that have been approved for -- by the FDA for release of product batches. 08:53:38 08:53:47 08:53:51

Q. And I guess I'm just trying to understand, based on your experience, I mean, what sorts of specification ranges -- what -- how would you describe that? 08:53:56 08:53:57 08:53:59 08:54:06

I'm not sure -- I want to use your terminology to make sure, when I say, you know, 40 milligrams plus or minus 10 percent or 20 million grams plus or minus 5 percent, that's what I'm trying to talk about. 08:54:09 08:54:10 08:54:12 08:54:15 08:54:19

I don't know if you call that tolerances. I don't know -- I don't know what you call it. What would you refer to that as? 08:54:21 08:54:22 08:54:24 08:54:25

MS. KAYALI: Objection. Foundation. 08:54:27 08:54:28

BY MR. KANE: 08:54:28

Q. Or just the specification? 08:54:28

A. Yeah, I think it's just part of the specification. 08:54:32 08:54:35

Q. Okay. And what I'm just trying to understand is based on your experience, staying with our discussion here, protein formulation, liquid protein formulation of an antibody, what range around the target have you seen? 08:54:37 08:54:39 08:54:44 08:54:49 08:54:54 08:55:04

Is it plus or minus 5, plus or minus 10, plus or minus 15, or some other number? 08:55:05 08:55:06

MS. KAYALI: Objection. Again, please don't reveal any third-party confidential specifications. To the extent you can answer without doing so, feel free. 08:55:11 08:55:12 08:55:18 08:55:20

A. And I just want to clarify just so I'm -- I have the right context of your question. I think you're just asking general background, not related to any specific opinion -- 08:55:24 08:55:27 08:55:30 08:55:32 08:55:34

BY MR. KANE: 08:55:36

Q. Correct. 08:55:36

A. -- in my report. 08:55:36

Q. Correct. 08:55:37

A. Okay. Again, I will -- I will repeat 08:55:38

what I've been told by the FDA and other regulatory bodies time and time again. I mean, in a certain sense, everyone wants, okay, I want a specific number so I know what to target. And the regulatory bodies actually, for good reason, don't -- I know there's always a concern that regulatory bodies create inflexibility. They're aware of that, and they want to promote flexibility as long as the product is safe and effective, so there's not any broad specification. 08:55:50 08:55:54 08:55:58 08:56:02 08:56:06 08:56:10 08:56:16 08:56:20 08:56:27 08:56:31 08:56:35

It really depends on the specific product and the justification of the filer. 08:56:37 08:56:38

Q. I understand that and I appreciate that. 08:56:44 08:56:45

So I'm just asking, though, on the specific product for specific filers that you have consulted with, without identifying any -- without giving, you know, those identities, what sort of values have you been aware of? 08:56:47 08:56:49 08:56:53 08:56:55 08:56:59 08:57:03

MS. KAYALI: Objection. Again, 08:57:05

please do not reveal a third-party's confidential specifications. If you can answer the question without doing so, go ahead. 08:57:05 08:57:09 08:57:10 08:57:13

A. I mean, for the reasons I mention, I don't have here -- frankly, I'm not sure -- I don't think this is part of my opinion, so I don't have specific numbers in my head. I'd have to go and refresh those numbers based on specific filings that I've seen, which generally are confidential, so I couldn't reveal. 08:57:17 08:57:24 08:57:29 08:57:30 08:57:33 08:57:37 08:57:42 08:57:45

Again, I think the point is, as I've emphasized, from the regulatory bodies, not to create an expectation that there is some specific range and specification, but to leave it up to the filer to propose that, the range, and to justify what that filer proposed. 08:57:47 08:57:53 08:57:57 08:57:59 08:58:04 08:58:09

BY MR. KANE: 08:58:16

Q. Let's go at it from a different direction. 08:58:16 08:58:17

You would agree with me that there's 08:58:20

going to be a certain amount of variability in a manufacturing process for a liquid protein-based formulation? 08:58:25 08:58:29 08:58:31

MS. KAYALI: Objection. Foundation. Vague. 08:58:34 08:58:35

A. You said it a different way. So you're talking about variability in the process? 08:58:45 08:58:47 08:58:49

BY MR. KANE: 08:58:49

Q. In the output. 08:58:49

A. Oh, in the output. 08:58:50

Q. So, and from batch to batch. You might have -- again, just to kind of give you the context of what I'm trying to get at here, if the target is 40 milligrams per milliliter of protein, Batch 1 might be 40.5 milligrams per milliliter. Batch 2 might be 39 milligrams per milliliter. Batch 3 might be 39.8 milligrams per milliliter. So there's a certain amount of variability in the manufacturing process, correct? 08:58:53 08:58:55 08:58:57 08:59:00 08:59:05 08:59:12 08:59:16 08:59:18 08:59:23 08:59:26

A. Maybe I'll -- I'm trying to help you 08:59:37

out. 08:59:41

You asked about product, and then you ended by asking about process. I think you're asking about the product as the output of the process, because when you're asking about process, we're also controlling process variables. 08:59:43 08:59:45 08:59:48 08:59:52 08:59:55 08:59:59

Q. I'm talking out the output. There's a variability in the output of the process. 09:00:01 09:00:04

MS. KAYALI: Dr. Trout, were you finished with your answer? 09:00:06 09:00:06

THE WITNESS: Yeah, that's fine. 09:00:09

MS. KAYALI: Okay. 09:00:10

A. There's generally going to be variability in any -- any sort of product that's manufactured. 09:00:14 09:00:16 09:00:20

BY MR. KANE: 09:00:25

Q. And in your experience in the industry, specifically let's say in protein manufacturing, which would include antibody manufacturing, what kind of range of variability have you observed? 09:00:25 09:00:25 09:00:33 09:00:36 09:00:42

MS. KAYALI: Objection. Foundation. Vague. Scope. 09:00:49 09:00:50

A. Again, I just don't have numbers on the top of my head. I don't think this was part of my opinions here. I appreciate your asking general background. 09:00:58 09:01:02 09:01:04 09:01:08

And again, on a high level, it's what I was saying. It's up to the manufacturer or the filer to propose to regulatory agencies what the specification is, including the plus or minus, the statistical range, and to justify that. 09:01:12 09:01:14 09:01:19 09:01:24 09:01:28 09:01:33

It's -- I know we all want specific numbers, but the regulatory agencies, rightly so, if you think about it, don't want to peremptorily constrain or in some cases not constrain what should be more constrained. 09:01:34 09:01:37 09:01:40 09:01:44 09:01:50

BY MR. KANE: 09:01:56

Q. Again, I'm not talking about regulatory agencies now. I'm just talking about what the output of a manufacturing process is that you have actually seen. 09:01:56 09:01:57 09:01:59 09:02:01

So, for instance -- I mean, I understand, for instance, there may be a regulatory specification plus or minus 10 percent. But the manufacturer might have a -- the ability and control the process to a tighter specification, say plus or minus 5 percent. So inside the plant, they're able to achieve plus or minus 5 percent on a very, say, regular basis, even if the regulatory specification is plus or minus 10. 09:02:10 09:02:13 09:02:14 09:02:17 09:02:22 09:02:26 09:02:28 09:02:31 09:02:35 09:02:37

And what I'm interested in, what I'm trying to get at, Doctor, just to help make sure we're on the same page, is in your experience, building pilot plans or the research that you've done or the consulting you've done, in this field, what sorts of tolerances are commonly or often achieved for these types of products? 09:02:40 09:02:42 09:02:43 09:02:47 09:02:52 09:02:54 09:03:04 09:03:13

MS. KAYALI: Objection. Scope. Vague. Foundation. 09:03:15 09:03:18

A. I'm not -- if I understand your question, I think what you're asking is if a 09:03:32 09:03:37

filer has approved certain specification with the statistical error, which I'm sure you're familiar, we call these "error." It doesn't mean it's a mistake. It's just what -- the scientific term for statistical variation. 09:03:42 09:03:48 09:03:52 09:03:54 09:03:58

If you're asking can it -- can it be lower on average than the specification, and I guess in theory, certainly, as long as it's within what was agreed to. And that's why I focus on what was agreed to with regulatory agencies, which is, hopefully and generally, based on science and engineering, that understanding. 09:04:03 09:04:07 09:04:15 09:04:19 09:04:22 09:04:25 09:04:30 09:04:34

Again, I -- I don't have numbers on the top of my head from specific instances. Again, I don't think it's in any of my opinions here. But I guess they could be -- as long as they're within an agreed-upon specification for release, I think they can be smaller. 09:04:38 09:04:42 09:04:44 09:04:46 09:04:51 09:04:53 09:04:57

BY MR. KANE: 09:05:12

Q. So, Doctor, we've been going about an 09:05:12

hour. Do you want to take a break or do you want to keep going? 09:05:14 09:05:16

A. I'm good, unless you need a -- 09:05:16

THE STENOGRAPHER: I'm good. 09:05:20

MR. KANE: We'll go for a little bit here. 09:05:22 09:05:23

BY MR. KANE: 09:05:23

Q. I think we discussed you're a chemical engineer, correct? 09:05:23 09:05:26

A. Yes. I mean, that's -- you could call me that, yes. 09:05:27 09:05:30

Q. And you're not an ophthalmologist? 09:05:32

A. Correct. 09:05:38

Q. And you've never administered ophthalmic drugs or given intravitreal injections to a patient? 09:05:39 09:05:43 09:05:46

A. That's correct. 09:05:50

Q. You are only providing opinions from the perspective of a product formulator? 09:05:57 09:06:03

A. I mean, I guess we should just use the terminology that's been agreed upon. I don't think there's any disagreement here. 09:06:40 09:06:43 09:06:46

Starting on page 34 of my report, that's the section on the person of ordinary skill in the art. I'm going to Paragraph 68. 09:06:50 09:06:55 09:07:02

I have in quotes, "The agreed-upon definition of this person of ordinary skill in the art." Number 1 is "the medical doctor in ophthalmology," and it continues. 09:07:12 09:07:13 09:07:18 09:07:22

As we established, I'm not a medical doctor in ophthalmology. And (2) is "a Ph.D. in pharmaceutical sciences or in a similar field, with at least several years of experience in the development, manufacture, and characterization of therapeutic proteins, including, for example, fusion proteins or antibodies." 09:07:24 09:07:27 09:07:32 09:07:35 09:07:37 09:07:40 09:07:43 09:07:46

And then in 69, just that it's all important as background, but I say, the last sentence, "I, thus, consider myself to have at least the qualifications of part (2) of the POSA definition above as of May 10, 2018." 09:07:48 09:07:52 09:07:57 09:07:59 09:08:03

So I would use the terminology that's there. 09:08:08 09:08:09

Q. And so in the multidisciplinary team identified in Paragraph 68, you consider yourself to be in the second part of that team, which is the "Ph.D. in pharmaceutical sciences or in a similar field," correct? 09:08:11 09:08:18 09:08:22 09:08:28 09:08:30

A. Correct. And I read -- 09:08:37

Q. Yes. 09:08:39

A. -- it continues but -- 09:08:40

Q. Understand. 09:08:41

A. -- yes, that's correct. 09:08:42

Q. And so you're offering your opinions from that perspective, not from the perspective of a medical doctor? 09:08:43 09:08:48 09:08:51

A. That's correct. And as I noted here, I think you asked some questions about Dr. Bressler before. I understand he is offering opinions with respect to the medical doctor, and I discuss this, for example, in my Paragraph 5. 09:09:08 09:09:12 09:09:16 09:09:20 09:09:26 09:09:30

Q. So you are not providing opinions on clinical issues such as dose selection, right? 09:09:41 09:09:45 09:09:50

MS. KAYALI: Objection. Vague. 09:09:56

A. So I think you might be referring, for example, to my Paragraph 99 on page 56. And I think there's similar statements like this. 09:10:19 09:10:23 09:10:32

I'll wait until you get there. 09:10:35

BY MR. KANE: 09:10:37

Q. Yes. 09:10:37

A. Okay. The header is "Dose," as you asked in your question. And I say, "I have no opinion on whether, from a clinical perspective, the POSA would have been motivated to use an 8 milligram dose of VEGF receptor fusion protein in the intravitreal formulation." 09:10:38 09:10:41 09:10:46 09:10:48 09:10:52 09:10:56 09:10:59

And then it continues there. I do want to emphasize, though, that certainly as a pharmaceutical scientist, to the extent that it's relevant, we would take into account clinical issues. I don't want to say I have nothing to do with clinical -- the clinical aspects of pharmaceuticals, but I'm certainly not a medical doctor or ophthalmologist, as 09:11:02 09:11:06 09:11:10 09:11:15 09:11:19 09:11:22 09:11:25 09:11:30

you asked, and would rely on the ophthalmologist for certain aspects and take those into account, as I've noted here farther down in this paragraph. 09:11:33 09:11:36 09:11:39 09:11:44

Q. If we look at Paragraph 189, page 126. 09:12:50

A. Got it. Got it. Okay. I am there. 09:13:12

Q. So this is another section on dose -- 09:13:18

A. Oh, I'm sorry. Just to -- I think it's 125 it starts, if I'm -- 09:13:20 09:13:22

Q. It starts on 125. You're correct. 09:13:25

A. Okay. Then I am there. 09:13:27

Q. I was going -- I'm going to ask you about the first sentence on the top of page 126. That's my mistake. 09:13:30 09:13:34 09:13:35

You say there that you "have been asked to assume for purposes of your opinions herein (without taking any position as to whether that assumption is correct) that a POSA would have a reason or motivation, from a clinical perspective, to use an 8 mg dose of VEGF receptor fusion protein." 09:13:40 09:13:41 09:13:45 09:13:49 09:13:52 09:13:55 09:14:01

Do you see that? 09:14:06

A. Yes. And I think you said "a POSA." 09:14:06
It says "the POSA," just to be clear, but yes. 09:14:09
Q. So at least for part of your analysis, 09:14:14
you made that assumption? 09:14:18
A. Yes. 09:14:28
Q. And you're not taking any position as 09:14:30
to whether that assumption is correct? 09:14:32
A. Yes. 09:14:42
Q. Kind of going back a little bit. In 09:15:09
your work on protein formulation development, 09:15:11
have the -- what routes of administration have 09:15:27
the products been delivered to a patient? 09:15:31
A. Again -- well, I do research at MIT. 09:15:48
I mean, most of my work in this area has been 09:15:58
research leading to publications in order to 09:16:02
advance the field of protein development and 09:16:05
stability. So it's research related to that. 09:16:10
So a lot of that research is not -- well, the 09:16:20
research itself -- well, let me back up. 09:16:21
We certainly have filed patents that 09:16:28
we hope will be useful, but the research -- 09:16:32
specific research leading to publications is 09:16:37

not intended directly to be administered, but certainly, the field of those products would include intravitreal injection, which I know is important here; subcutaneous injection, which is actually also important here; and intravenous injection, for example. Intramuscular also, I would say. 09:16:41 09:16:44 09:16:49 09:16:54 09:16:59 09:17:03 09:17:08

I've also worked in the area of other -- other types of injections, but those would be the main four. 09:17:12 09:17:13 09:17:19

Q. In terms of the protein formulation development, does the route -- how does the route of administration impact -- let me ask this question, how does the route of administration impact your work on protein formulation development? 09:17:36 09:17:39 09:17:41 09:17:44 09:17:46 09:17:50

MS. KAYALI: Objection. Vague. 09:17:53

A. And I should emphasize, if we're talking about my research at MIT, I think it's fine to call it "protein development" as long as it's understood it's protein development research. MIT doesn't develop commercial 09:17:58 09:18:02 09:18:05 09:18:09 09:18:11

products as such. 09:18:16

I mean, that's just a very general 09:18:20

question. I think it's a fine question at a 09:18:24

high level. I would say that the development 09:18:28

scientist would take into account the route of 09:18:35

administration among a whole variety of other 09:18:41

aspects in developing a product. It, 09:18:45

certainly, would take into account the route 09:18:48

of administration. 09:18:51

BY MR. KANE: 09:19:01

Q. You mentioned a minute ago that part 09:19:01

of your research was focusing on stability of 09:19:04

the formulations? 09:19:10

A. Yes. 09:19:14

Q. What does it mean for a formulation to 09:19:16

be stable? 09:19:17

MS. KAYALI: Objection. Vague. 09:19:20

A. I mean, at a high level, chemical 09:19:29

products, including -- well, components of 09:19:38

products like proteins tend to degrade, and 09:19:41

it's almost -- well, you asked specifically 09:19:53

about, I think, protein formulations, probably 09:19:55

the case across the board, certainly in pharmaceuticals, and part of the objective, again, focusing on the MIT research, again, I've done extensive consulting also, but focusing on MIT research is to understand these routes of degradation better, and based on that understanding, try to hinder them. 09:20:00 09:20:03 09:20:08 09:20:11 09:20:17 09:20:19 09:20:25

And that's one way -- I think a good way of thinking about stabilization. 09:20:30 09:20:33

BY MR. KANE: 09:20:49

Q. Is there a -- is there a set criteria for a formulation to be considered stable -- a protein formulation to be considered stable? 09:20:49 09:20:54 09:20:55

MS. KAYALI: Objection. Vague. 09:20:59

A. I would say in general, yes. This is going to, again, depend on -- now I think we're talking commercial products or products intended for that, because in terms of research, we'll look at kinetics and whatnot and try to hinder those kinetics or understand them. 09:21:07 09:21:13 09:21:16 09:21:21 09:21:24 09:21:28 09:21:31

In terms of commercial products, 09:21:33

again, there would be certain specifications, and some of those specifications, I think we talked about release specifications, but other specifications would have to do with the stability as such over time, for example. 09:21:35 09:21:40 09:21:43 09:21:47 09:21:52

BY MR. KANE: 09:21:58

Q. And are those specifications similar to the release specifications variable between different products? 09:21:58 09:22:00 09:22:10

MS. KAYALI: Objection. Foundation. 09:22:18 09:22:20

A. I wouldn't quite say they're variable. I mean, if you mean that different products can have different specifications, certainly, again, as I've emphasized, and as regulatory bodies have emphasized to me, it's up to the filer to make the case for the desired specification, including stability. 09:22:25 09:22:28 09:22:29 09:22:35 09:22:42 09:22:48 09:22:51

BY MR. KANE: 09:23:00

Q. Can the excipients used in the formulation affect stability? 09:23:00 09:23:02

A. Yes. I mean, that's part of 09:23:11

formulation is to develop a product. In this case, we're talking about proteins together with the excipients, and the excipients can also degrade, of course. So that's part of the concern of a formulation scientist. 09:23:14 09:23:20 09:23:22 09:23:28 09:23:31

Q. Can the pH of the formulation affect stability? 09:23:35 09:23:37

MS. KAYALI: Objection. Form. 09:23:42

A. I mean, certainly we're just talking about a high level. I mean, I talk about pH here. pH can affect stability of a protein formulation. 09:23:54 09:23:58 09:24:00 09:24:03

BY MR. KANE: 09:24:06

Q. Can temperature affect the stability of the protein formulation? 09:24:06 09:24:07

A. Yes, again, at a high level, temperature can have an effect. Typically -- typically, some exceptions, but typically processes, including degradation processes, are faster at higher temperatures, slower at lower temperatures. 09:24:20 09:24:22 09:24:26 09:24:29 09:24:33 09:24:37

Q. And since you've discussed they're 09:24:42

faster and slower, is time an element of determining whether or not a formulation is stable? 09:24:44 09:24:48 09:24:51

MS. KAYALI: Objection. Vague. Scope. 09:24:54 09:24:58

A. I should emphasize, as I've understood your questions about stability, I was taking into account time. I think it has to do with time. If you mean the product changes over time, then yes, that's the point. 09:25:03 09:25:06 09:25:09 09:25:14 09:25:18

BY MR. KANE: 09:25:23

Q. And, for instance, the stability specifications could have different time points? There could be one product with a 6-month stability specification, and another product with a 12-month, another product with a 24-month specification, correct? 09:25:23 09:25:26 09:25:28 09:25:36 09:25:38 09:25:41

MS. KAYALI: Objection. Foundation. 09:25:43 09:25:44

A. Again, you're talking about commercial products? 09:25:55 09:25:59

BY MR. KANE: 09:26:00

Q. Correct. 09:26:00

A. I mean, certainly, I guess in broad 09:26:01

terms, it depends on the area, but certainly 09:26:06

different products can have different 09:26:12

specifications, different times. You're 09:26:17

asking that just at a high level. 09:26:22

Q. Yes. You mentioned degradation 09:26:25

pathways. Are there primary degradation 09:26:37

pathways that a formulator takes into account 09:26:45

when creating a protein formulation? 09:26:49

A. I would say, depending on the protein 09:27:06

and the application and different aspects, the 09:27:12

formulation -- you know, we call it 09:27:21

preformulation, although it's not necessarily 09:27:22

a defined wall between preformulation and 09:27:29

formulation. But often in preformulation, we 09:27:32

would attempt to find what are the important 09:27:37

routes of degradation to identify those and 09:27:40

address them in various ways. This could also 09:27:46

be before preformulation. 09:27:49

Q. Is deamidation a degradation pathway 09:27:59

that can occur? 09:28:02

A. Broadly speaking, proteins can be subject to deamidation as products in the body. You might be aware, I've published several papers in that area. 09:28:13 09:28:16 09:28:20 09:28:25

Q. Is aggregation a degradation pathway? 09:28:28 09:28:31

MS. KAYALI: Objection. Vague. 09:28:35

A. Again, at a high level, aggregation is a potential degradation route for protein products. 09:28:41 09:28:44 09:28:51

BY MR. KANE: 09:28:55

Q. And I think you say in Paragraph 85 of your declaration that by 2018 there were strategies for stable -- 09:28:55 09:29:00 09:29:02

A. Sorry, let me -- just wait until I get there. 09:29:04 09:29:05

Okay. Thank you. I'm there. 09:29:14

Q. I'll get there myself. 09:29:15

You see in the first sentence, you state that by 2018 -- well, you don't say "by 2018," but there are strategies for attempting to stabilize therapeutic proteins against 09:29:23 09:29:24 09:29:30 09:29:35

aggregation, correct? 09:29:37

A. Yes, I say that. And I think it's 09:29:51

important to understand that certainly we have 09:29:52

a range of approaches as a formulation 09:29:58

scientist, how they end up affecting a 09:30:02

particular formulation as of 2018, for 09:30:09

example, you mentioned, would not have been 09:30:12

predictable. 09:30:17

Q. What do you mean, they would not have 09:30:25

been predictable? 09:30:27

A. Okay. Let me clarify. Perfectly 09:30:33

fine. 09:30:37

What I mean is that there were 09:30:38

approaches, what we would consider generally 09:30:43

approaches to attempt to address aggregation 09:30:46

in a particular protein application. One 09:30:51

couldn't predict ahead of time whether those 09:30:57

approaches would work for a specific 09:31:00

application. So we have kind of general 09:31:04

approaches that have been developed over 09:31:07

decades really, but how it would affect a 09:31:09

specific protein in a specific environment 09:31:13

wouldn't have been predictable ahead of time to be part of an empirical project. 09:31:17 09:31:19

Q. When you began this work 30-some years ago, there weren't a lot of the biopharmaceuticals on the market, correct? 09:31:38 09:31:42 09:31:48

MS. KAYALI: Objection. Vague. 09:31:53

A. I don't have the number, but certainly in the past 30 years, the number of biopharmaceuticals has increased significantly. 09:31:53 09:32:02 09:32:06 09:32:09

BY MR. KANE: 09:32:12

Q. And in particular, if we look at the -- say, the monoclonal antibody space, that has certainly increased significantly in the last 30 years, agree? 09:32:12 09:32:15 09:32:19 09:32:22

MS. KAYALI: Objection. Vague. 09:32:28

A. Again, at a high level, the number of monoclonal antibody products has, yes, increased over the past 30 years. 09:32:28 09:32:35 09:32:38

BY MR. KANE: 09:32:41

Q. Do you know when the first fully humanized monoclonal antibody was approved by 09:32:41 09:32:42

FDA? 09:32:45

A. I probably did know that at some 09:32:51

point, and I don't have that in the top of my 09:32:55

head. I would have to look -- 09:32:57

Q. It's been in the last 30 years, 09:32:59

though, you would agree with me? Do you 09:33:00

remember? 09:33:03

A. I would have to remember exactly when 09:33:09

that was. The first products were approved in 09:33:11

the '80s. And then as you indicated, there 09:33:18

was sort of a slow approval, a number of 09:33:20

products approved, and then that continued to 09:33:24

increase over the decades. 09:33:26

Q. Based on your experience, would you 09:33:43

agree with me that many of the monoclonal 09:33:46

antibody products developed in the early -- in 09:33:51

the 2000 or early 2000 time frame had 09:33:55

concentrations of less than 50 mgs per mL? 09:34:00

A. You said five zero? 09:34:09

Q. Yes. 09:34:11

A. Less than five zero? 09:34:11

Q. Five zero. 09:34:12

A. And specifically monoclonal antibodies? 09:34:14 09:34:15

Q. Correct. 09:34:16

MS. KAYALI: Counsel, sorry the transcript just reflects a different number, so I want to be very -- maybe it might be prudent to restate the question. 09:34:19 09:34:20 09:34:21 09:34:25

MR. KANE: Yeah, okay. 09:34:27

BY MR. KANE: 09:34:28

Q. Based on your experience, would you agree with me that many of the monoclonal antibodies -- antibody products developed in the early 2000 time frame had concentrations of less than 50 mgs per mL? 09:34:28 09:34:30 09:34:33 09:34:36 09:34:39

A. So sorry, just making sure we're happy with the transcription. 09:34:48 09:34:50

I assume you mean like around 2000, 2002-ish, this time frame? 09:34:54 09:34:59

Q. Yes. 09:35:01

A. Off the top of my head, that sounds fair. I mean, we could obviously check those numbers. 09:35:07 09:35:08 09:35:13

Q. And just generally, would you agree with me that the technology has developed such that there are now many -- several products on the market that have concentrations greater than 100 mgs per mL? 09:35:14 09:35:15 09:35:20 09:35:27 09:35:31

MS. KAYALI: Objection. Vague. 09:35:35

A. You're talking about now, 2026? 09:35:38

BY MR. KANE: 09:35:41

Q. Yes. 09:35:41

A. Well, let me -- it's kind of a two-part question. 09:35:45 09:35:50

I would say yes, sitting here, I think there are many -- several products, at least, that are formulated -- sorry, protein therapeutic products that are formulated at greater than 100 or you said 100 or greater, I think, mgs per mL. 09:35:53 09:36:01 09:36:04 09:36:08 09:36:11 09:36:16

I would say that our understanding has certainly advanced over, I think -- well, 20-ish plus years, as you've been alluding to. Yes, so if that's what you're asking. 09:36:20 09:36:26 09:36:32 09:36:38

Q. Okay. 09:36:40

MR. KANE: Why don't we take a break. 09:36:45 09:36:47

THE WITNESS: Okay. 09:36:47

THE VIDEOGRAPHER: This is the end of Media Number 1. We are going off the record. The time is 9:37 a.m. 09:36:48 09:36:48 09:36:51

09:50:48

(Recess taken from 9:37 a.m. to 9:51 a.m.) 09:50:48 09:50:48

09:50:55

THE VIDEOGRAPHER: This is the beginning of Media No. 2. We are going back on the record. The time is 9:51 a.m. 09:50:55 09:50:56 09:50:59

BY MR. KANE: 09:51:03

Q. Welcome back, Dr. Trout. 09:51:03

A. Thank you. 09:51:05

Q. You mentioned before the break preformulation work. 09:51:06 09:51:09

Do you recall that? 09:51:11

A. Yes. 09:51:15

Q. Okay. And can you describe what preformulation work is? 09:51:17 09:51:18

A. Yes. Again, as I stated, there's not necessarily a defined wall between, let's say, preformulation and formulation on the one hand, I should add discovery on the other. But broadly speaking, in preformulation -- I brought that up because you were specifically asking about routes of stability -- and generally during preformulation, one does initial analyses to understand potential routes of degradation and some initial characterization and whatnot. 09:51:24 09:51:32 09:51:34 09:51:37 09:51:42 09:51:46 09:51:48 09:51:54 09:51:58 09:52:06 09:52:11

Of course, new routes can come up during formulation, but that's, roughly speaking, preformulation. 09:52:15 09:52:18 09:52:23

Q. And so what -- in more detail, what is done to understand potential routes of degradation or otherwise characterize the molecule? 09:52:28 09:52:33 09:52:36 09:52:40

A. Well, I -- again, without any revealing confidential information, I've consulted for quite a few companies, and I would say the number of approaches is probably 09:52:45 09:52:50 09:52:53 09:52:55

more than the number of companies. Maybe it's the number of researchers or departments or whatever, so different people have different approaches. 09:53:02 09:53:07 09:53:09 09:53:12

But at a high level, a scientist would investigate the protein and get a -- start to get an initial sense of what kind of degradation routes could be a concern -- would be -- sorry -- what kind of degradation routes the formulation scientist would need to address. 09:53:14 09:53:22 09:53:30 09:53:34 09:53:40 09:53:43 09:53:47

I think you were asking about sort of the primary routes, so that would be where initial understanding of routes of degradation that would likely need to be addressed. 09:53:48 09:53:49 09:53:53 09:53:58

Q. Would part of that involve studying the molecule's reaction at different pHs? 09:54:04 09:54:07

MS. KAYALI: Objection. Vague. 09:54:12

A. What do you mean by "reaction"? 09:54:17

BY MR. KANE: 09:54:18

Q. Well, the degradation pathway responses that might be observed at different 09:54:19 09:54:20

pHs. 09:54:25

A. I would say that pH is something that 09:54:27
a skilled person would take into account early 09:54:35
on and throughout the development process. 09:54:39
Again, like everything else in this field, 09:54:43
there might be exceptions, but just as a 09:54:45
high-level general rule, pH would be taken 09:54:48
into account and continue to be taken into 09:54:52
account. 09:54:55

Q. Would, in the preformulation work, 09:55:01
different excipients be tested against the 09:55:05
molecule? 09:55:09

MS. KAYALI: Objection. Vague. 09:55:13

A. Again, now we're getting to the 09:55:13
potential, let's say, transition from 09:55:24
preformulation to formulation. Different 09:55:31
companies may put the testing of excipients in 09:55:34
different categories, but some companies 09:55:38
would -- or scientists, we could say, would 09:55:42
perhaps start testing the effects of 09:55:47
excipients. 09:55:53

BY MR. KANE: 09:55:55

Q. And so that, for instance, would include buffer, different buffers? 09:55:55 09:55:58

MS. KAYALI: Objection. Foundation. 09:56:02 09:56:07

A. I mean, I think it's up to the researcher. 09:56:07 09:56:10

BY MR. KANE: 09:56:17

Q. But it could include testing the molecule with different buffers? 09:56:17 09:56:20

A. One could test a molecule with different buffers. And I'm sure you've read in my report, I have a discussion -- significant discussion of proteins as their own buffers, but I think I understood your question to mean other buffers which could be incorporated into preformulation. 09:56:26 09:56:30 09:56:33 09:56:36 09:56:41 09:56:44 09:56:50

Q. And whether it's formulation or preformulation, that's not the important distinction I'm trying to make here. 09:56:55 09:56:56 09:56:59

A. Oh, oh. 09:57:01

Q. It's whether the molecule at some point -- the formulator at some point would 09:57:02 09:57:04

test the molecule with different excipients, including different buffers, that might be applicable. 09:57:06 09:57:12 09:57:15

MS. KAYALI: Objection. Vague. Foundation. 09:57:19 09:57:19

A. I mean, I guess in theory one could formulate a biologics formulation without any excipients. I think it depends on the formulation. 09:57:23 09:57:31 09:57:37 09:57:41

Of course, my work has involved primarily -- well, not just the effect of excipients, but also degradation of proteins in the absence of excipients. 09:57:43 09:57:47 09:57:49 09:57:53

BY MR. KANE: 09:58:00

Q. Well, at some point the formulator has to -- oftentimes the formulator will choose a buffer for the formulation, correct? 09:58:00 09:58:03 09:58:10

MS. KAYALI: Objection. Vague. Foundation. 09:58:12 09:58:22

A. I mean, since we're talking about buffers, I think that's a key part of the written description discussion that I have 09:58:40 09:58:42 09:58:48

starting on page 161, but also 217. Again, one could include a buffer or not. 09:58:53 09:59:02

I mean, I say that about six lines down from -- on page 218. Certainly buffers are in the toolbox of the skilled person. 09:59:07 09:59:10 09:59:20

BY MR. KANE: 09:59:22

Q. Okay. 09:59:22

A. But also the protein can buffer, and I have certainly a lot of discussion on that. 09:59:22 09:59:27

Q. Okay. Let's talk about, say, a stabilizer like a sucrose or some other mannitol, some other type of stabilizer along those lines. Are those tested against the molecule -- 09:59:30 09:59:32 09:59:39 09:59:43 09:59:45

MS. KAYALI: Objection. Vague. 09:59:47

BY MR. KANE: 09:59:47

Q. -- as part of preformulation or formulation characterization? 09:59:47 09:59:48

MS. KAYALI: Objection. Vague. 09:59:51

A. Again, I think it's fine to use the term "stabilizer" as long as it's clear in the context, because different excipients can do 09:59:56 09:59:58 10:00:02

multiple -- or a given excipient can do multiple things, and sometimes it's called something, I have a lot of discussion about that, and it does perhaps what it's called, but it does other things too at the same time. 10:00:09 10:00:12 10:00:16 10:00:17 10:00:22

But again, I mean, certainly I think one could say often excipients are tested during -- we want to call it the whole formulation process, including preformulation, as we've been discussing, and formulation. 10:00:29 10:00:32 10:00:36 10:00:38 10:00:44

BY MR. KANE: 10:00:49

Q. And if it's going to be a therapeutic product subject to FDA approval, would the formulator start with at least previously FDA-approved excipients? 10:00:49 10:00:50 10:00:54 10:01:00

MS. KAYALI: Objection. Foundation. 10:01:08 10:01:08

A. Just -- I think I understand what you're saying. Just a qualification on that, people use that term "FDA-approved excipients" as a shorthand. 10:01:14 10:01:17 10:01:25 10:01:28

I think -- I think what you're asking 10:01:30

is excipients on the inactive ingredients database, which means excipients that were or are in approved formulations. Just a small point. 10:01:31 10:01:35 10:01:40 10:01:44

So it's not the excipients that are -- that are approved per se, it's the formulation, and the excipient is in the formulation. 10:01:45 10:01:47 10:01:50 10:01:52

And I think -- 10:01:55

Q. You understood what I was asking. 10:01:55

A. Yeah, I just -- but I wanted to make that clear, to make sure I understood. 10:01:57 10:01:58

And I think certainly there would be a tendency towards using excipients if one were going to implement them, that had been in approved products, approved as you want to say shorthand. I mean, clearly innovation is made by using excipients, either new excipients or excipients that may be in the inactive ingredients database for, let's say, other approaches, broadly speaking, and delivery routes, for example, or other approaches, and 10:02:09 10:02:11 10:02:15 10:02:21 10:02:25 10:02:27 10:02:32 10:02:35 10:02:40 10:02:46

then using them in a new approach. 10:02:48

So I think it just really depends on 10:02:52

the development approach. 10:02:56

Q. Okay. We've talked some about 10:02:58

aggregation already. How would the formulator 10:03:00

go about studying the aggregation pathway 10:03:06

parameters in deciding on a formulation? 10:03:10

MS. KAYALI: Objection. Vague. 10:03:16

A. Just -- you added "parameters." I 10:03:18

think you may have just meant "aggregation," 10:03:26

but what do you mean by "parameters"? 10:03:28

BY MR. KANE: 10:03:30

Q. I just meant aggregation, yeah, sorry. 10:03:30

So yeah, how would a formulator go about 10:03:33

studying the aggregation pathway when 10:03:35

developing a formulation? 10:03:38

A. Well, that's where I'm sort of 10:03:40

questioning the premise. You say "the 10:03:45

aggregation pathway." What do you -- 10:03:49

Q. Well, I understand there's a -- well, 10:03:51

what is aggregation? 10:03:53

A. Aggregation generally means that 10:03:59

there's a protein-protein interaction, such that just say they're attached. It can be reversible/irreversible. It can be native/nonnative, for example. 10:04:04 10:04:08 10:04:14 10:04:18

I teach a course on this, and we go through all kinds of different terms. Some terms mean similar things, but there's all kinds of different, let's say, ways of describing various aspects of aggregation. 10:04:22 10:04:24 10:04:26 10:04:28 10:04:32

Q. Okay. In terms of making the formulation more stable, what aspect of aggregation is important? 10:04:36 10:04:37 10:04:45

MS. KAYALI: Objection. Vague. 10:04:49

A. I mean, I guess all aspects are potentially important, and it depends on the given situation, protein, et cetera. That's why I have a whole section on aggregation in my short course. 10:04:52 10:05:03 10:05:07 10:05:15 10:05:20

BY MR. KANE: 10:05:22

Q. Are there other ways to measure aggregation in a liquid protein formulation? 10:05:22 10:05:23

A. Yes. There are various analytical 10:05:32

methods that can be employed. 10:05:34

Q. And what are those analytical methods? 10:05:38

A. I mean, I have a whole section on 10:06:16
protein aggregation in my report starting on 10:06:19
page 40. I have various references. 10:06:23

One of the -- I think I may not 10:06:30
explicitly refer to -- well, not a lot of 10:06:33
methodologies here. I do refer to DSC, 10:06:41
differential scanning calorimetry, on the top 10:06:48
of page 44. That's one of the methods that 10:06:50
can be employed, and certainly I can explain 10:06:53
that more. 10:06:57

These papers are going to include size 10:06:59
exclusion chromatography, which is another 10:07:08
method. You know, as aggregation proceeds, 10:07:12
even particulates can form. You can consider 10:07:18
those sort of large aggregates. I mean, there 10:07:23
are other methods that can be employed for 10:07:28
those. 10:07:30

Again, I can go through a lot. I 10:07:31
don't know if you want a list off the top of 10:07:34
my head, but one is just visual. So a visual 10:07:36

inspection is one method. These papers refer to a bunch of methods. I have -- there are tables of various methodologies, for example. 10:07:40 10:07:44 10:07:47 10:07:50

Q. In your experience, is SEC commonly used in the industry to measure aggregation? 10:07:51 10:07:53

A. Just -- SEC? 10:07:58

Q. Yes, yes. Well, did I say it wrong? 10:08:01

A. No, no. Again, it's fine, I'll clarify, sometimes it's a little hard to hear you. I thought you may have said SCC. 10:08:04 10:08:09 10:08:11

Q. No. 10:08:14

A. But you mean SEC? 10:08:14

Q. Yes. 10:08:17

A. Certainly that's a method that is used, I would say, quite often. That was my, sort of, answer. That was one of the methods I mentioned, size exclusion chromatography. 10:08:19 10:08:23 10:08:29 10:08:31

Q. And what is size exclusion chromatography telling the formulator about the formulation in the context of aggregation? 10:08:41 10:08:42 10:08:48 10:08:51

A. Well, in size exclusion chromatography, you'll -- you inject a sample into the chromatographic column, and then -- it's size exclusion. Large particulates can be excluded, but others are not excluded, but the rate at which they go through the column will depend on the size and because of the effect of size on interactions with the column. 10:08:56 10:09:01 10:09:06 10:09:17 10:09:23 10:09:28 10:09:31 10:09:36 10:09:39

And then typically one uses a methodology to detect proteins coming out of the column. So the size exclusion chromatography is the method of separating based on size, again, realizing it uses the term "exclusion," but it's really a separation. 10:09:41 10:09:43 10:09:50 10:09:54 10:09:57 10:10:01 10:10:04

It doesn't -- it excludes only very large particulates, and then determining different aggregates and fragments, so based on size or you could say molecular weight. 10:10:06 10:10:08 10:10:13 10:10:16

Q. Okay. And you -- we talked earlier, there are strategies that a formulator has in 10:10:34 10:10:35

order to stabilize therapeutic proteins against aggregation? 10:10:45 10:10:46

A. Yes. Again, as I emphasized, we luckily are not starting with a complete blank slate. We have methodologies, as you've been asking me about. 10:10:52 10:10:58 10:11:02 10:11:05

There are categories of excipients, and we talked about those. You mentioned stabilizers. So there -- you know, there are broad approaches that formulators have developed over the decades. 10:11:08 10:11:09 10:11:14 10:11:18 10:11:20

But again, their applicability to a particular protein in a particular environment as of even today, I published lots of papers on this that we can discuss, but wouldn't be predictable without empirical work. 10:11:23 10:11:28 10:11:32 10:11:40 10:11:43

I can explain what that means if you want, because you may have seen, many of my papers I attempt to develop predictive models, but that's -- that would be a high-level answer to your question. 10:11:46 10:11:48 10:11:49 10:11:53 10:11:57

Q. Okay. As part of this formulation or 10:11:59

preformulation work, would viscosity be studied? 10:12:18 10:12:21

MS. KAYALI: Objection. Vague. 10:12:23

A. I assume you mean today. You're talking -- the time frame may make a difference, but... 10:12:24 10:12:33 10:12:35

BY MR. KANE: 10:12:38

Q. Well, say 2018. 10:12:38

A. Okay. Thank you for clarifying. 10:12:39

I think it really depends. If there's a reason that the pharmaceutical scientist thinks that viscosity needs to be addressed, then the scientist would address it. If there's no reason, then the scientist wouldn't address it. 10:12:46 10:12:50 10:12:53 10:12:56 10:13:01 10:13:04

The biggest constraint in a company are resources of scientists' time. 10:13:06 10:13:10

Q. If the product was -- yeah, if the product in development was intended to be subcutaneously injected, would the formulation scientist look at viscosity? 10:13:14 10:13:18 10:13:25 10:13:29

MS. KAYALI: Objection. Vague. 10:13:31

A. Again, I would think in general, the scientist would think and consider about viscosity and whether that needs to be explicitly studied or not. 10:13:31 10:13:38 10:13:42 10:13:45

If by "study" you mean doing experiments on viscosity and the effect of excipients, I think that would depend on the application. But if you're asking would it be in the mind of a formulation scientist, I would say yes. It depends on whether the scientist thinks it needs to be actually studied empirically or not. 10:13:49 10:13:51 10:13:53 10:13:55 10:13:58 10:14:01 10:14:05 10:14:07

Q. When would the scientist think that it needs to be studied empirically? 10:14:09 10:14:10

A. If the scientist thinks that it's going to be a concern for the given -- for a given application that the scientist has been tasked with. 10:14:19 10:14:21 10:14:25 10:14:28

Q. Okay. And I gave you one example about subcutaneous injection. Would that be an application that would raise a concern with respect to viscosity? 10:14:30 10:14:31 10:14:34 10:14:38

MS. KAYALI: Objection. Vague. 10:14:42

A. Sorry. Just to be clear, I was answering -- after you mentioned subcutaneous injection, I was answering your question with that in mind. I presume you were asking me about subcutaneous. 10:14:42 10:14:46 10:14:49 10:14:52 10:14:55

BY MR. KANE: 10:14:56

Q. Okay. It wasn't clear from your answer. 10:14:56 10:14:59

A. Oh, okay. I'm sorry, yeah. 10:15:00

Q. Would the same be true with intravitreal? 10:15:03 10:15:06

A. Yes, the same would be true. 10:15:10

Q. So the scientist or the formulator may or may not need to test viscosity for an intravitreal product? 10:15:15 10:15:19 10:15:22

A. Broadly speaking, I think that there is -- if there's any rule in formulation scientist is that there are no set rules. 10:15:28 10:15:33 10:15:36

But I would certainly think viscosity, typically intravitreal injection, I think we all know is done with very small needles, and 10:15:40 10:15:43 10:15:47

it's not a pleasant process. You may have seen pictures, no injection is, but intravitreal is something that one -- the formulation scientist would be concerned about. So I would think viscosity would be something very much on the mind of a formulation scientist. 10:15:56 10:15:59 10:16:02 10:16:05 10:16:06 10:16:12 10:16:14

Q. So formulation scientists developing an intravitreal product would likely test viscosity? 10:16:19 10:16:22 10:16:25

MS. KAYALI: Objection. Vague. 10:16:28

A. I think it depends on the application. You're asking a very high level, but I'm just trying to give you a comparison. 10:16:32 10:16:35 10:16:38

I think that the formulation scientist would think more about the potential effects of viscosity on intravitreal injection versus subcutaneous, again, sort of not like a hard rule, but I think generally that would be a significant concern because of the small bore size of needles typical for intravitreal injection. 10:16:40 10:16:46 10:16:52 10:16:57 10:16:59 10:17:03 10:17:06 10:17:10

BY MR. KANE: 10:17:14

Q. Do you know the bore size of needles typical for subcutaneous injection? 10:17:14 10:17:16

A. Again, we're talking about 2018 here? 10:17:19

Q. Yes. 10:17:22

A. Again, I am familiar with the bore sizes for subcutaneous injection. Again, it depends on the application. 10:17:28 10:17:31 10:17:35

Often -- in general, we want -- smaller bore size is better because of concerns of -- the formulation scientist would be aware of pain on injection. I mean, I think we all agree, getting shots is not pleasant, so it would be nice to get to 26 or 24. I'd like to go lower, but I'm sure there are bore sizes that are larger for subcutaneous as of 2018. 10:17:40 10:17:43 10:17:47 10:17:51 10:17:56 10:17:59 10:18:06 10:18:11 10:18:14

Q. Are there -- are there bore sizes that are smaller than 26 for subcutaneous? 10:18:18 10:18:21

MS. KAYALI: Objection. Vague. 10:18:24

A. I'd have to do an analysis. Nothing's coming to the top of my head. 10:18:25 10:18:30

I guess I'm thinking about projects I've worked on. That's why I mentioned I think it's confidential, just the fact of bore sizes 24 and 26 and also larger ones. I don't recall, sitting here, having worked on subcutaneous with a bore size of 30. 10:18:33 10:18:35 10:18:37 10:18:40 10:18:46 10:18:48

BY MR. KANE: 10:18:52

Q. You what? 10:18:52

A. Oh, I -- I thought I was trying to project. Apologies. 10:18:54 10:18:56

Sitting here, it's not coming to my mind a project with a bore size of 30 for subcutaneous injection. I'm just remembering 24 and 26 and larger than that, but, you know, one could do that analysis and determine if that's the case. 10:19:00 10:19:04 10:19:08 10:19:13 10:19:20 10:19:23

Q. So really, it's not necessarily intravitreal versus subcutaneous. It's the bore size of the needle used that would influence the thinking of the formulator? 10:19:24 10:19:30 10:19:32 10:19:36

MS. KAYALI: Objection. Foundation. Vague. 10:19:40 10:19:41

A. I don't think that's a fair summary of what I -- what I said. 10:19:48 10:19:50

BY MR. KANE: 10:19:52

Q. Well -- 10:19:52

A. Do you want me to go back? 10:19:52

Q. Let me give you a hypothetical. 10:19:53

Let's say I have a subcutaneous injection with a 29-gauge needle or an intravitreal injection -- or alternatively, I'm developing a product for intravitreal injection with a 29-gauge needle. 10:19:56 10:19:56 10:20:00 10:20:02 10:20:05

Does it matter whether one is subcutaneous in 29-gauge versus intravitreal in 29-gauge from the formulator's perspective? 10:20:09 10:20:11 10:20:14

MS. KAYALI: Objection. Foundation. Vague. 10:20:19 10:20:19

A. So I -- I don't think that that's a hypothetical that's representative of how the formulation scientist would think about the approach. 10:20:31 10:20:35 10:20:40 10:20:42

I think that there's more flexibility -- the choice of the bore size 10:20:44 10:20:46

would be part of what a -- the choice itself would be part of what a formulation scientist would take into account. So there's more flexibility for subcutaneous, if that's the goal, versus intravitreal, as we've been discussing. 10:20:50 10:20:56 10:20:59 10:21:05 10:21:07 10:21:12

So I don't think one would just say, okay, here's the bore size, but there would be trade-offs, and one would think about -- 10:21:13 10:21:14 10:21:18

BY MR. KANE: 10:21:21

Q. I understand. I guess what I'm saying is -- I'm just trying to isolate where the shot was being given by saying, the project is going to be a 29-gauge needle, that's determined, we're not debating that. 10:21:21 10:21:23 10:21:26 10:21:29 10:21:32

Does it matter whether that shot -- from the formulation perspective with respect to viscosity, does it matter whether that is going to be administered subcutaneously with that 29-gauge needle or intravitreally with that same 29-gauge needle? 10:21:36 10:21:38 10:21:39 10:21:42 10:21:44 10:21:47

MS. KAYALI: Objection. Vague. 10:21:51

Foundation. 10:21:53

A. I'm trying to emphasize it's not a realistic hypothetical. I don't know of any situation where the formulation scientist is given an input for subcutaneous that the needle has to be 29. That's what I'm -- the whole field, there's -- one tries to come up with the best solution that will help patients, will have efficacy and be safe, and fulfill the patient experience, and there's more flexibility for subcutaneous in terms of bore size than intravitreal. 10:21:58 10:22:03 10:22:04 10:22:08 10:22:12 10:22:16 10:22:20 10:22:24 10:22:28 10:22:30 10:22:34

Q. I understand that, Doctor, but that's not my question. 10:22:37 10:22:38

My question is, if it's then decided that there's going to be a 29-gauge needle used for subcutaneous versus a 29-gauge needle used for intravitreal, is it the 29-gauge needle that drives the thinking of the formulator with respect to viscosity, or is it the route of administration that drives the thinking of the formulator? 10:22:40 10:22:44 10:22:47 10:22:56 10:22:59 10:23:01 10:23:04 10:23:05

MS. KAYALI: Objection. Vague. Lacks foundation. 10:23:10 10:23:11

A. Okay. I'll try to answer your hypothetical as best I can, again noting that I don't think it's a realistic hypothetical for the reasons I mentioned. 10:23:16 10:23:20 10:23:24 10:23:27

But if for some reason you're giving me this constraint, I would say that the skilled person would take into account what we call the patient experience, which includes the injection per se, not just the needle. So I think all these would be factors in what we call the patient experience. 10:23:29 10:23:31 10:23:35 10:23:38 10:23:41 10:23:45 10:23:49

BY MR. KANE: 10:23:57

Q. Okay. But again, I'm asking -- and how does patient experience relate to viscosity from the formulator's perspective? 10:23:57 10:24:01 10:24:06

A. Okay. I certainly can answer that. I just want to be clear, in the previous question when I mentioned patient experience, I was addressing the bore size hypothetical. 10:24:11 10:24:14 10:24:17 10:24:19

Q. Okay. 10:24:23

A. So just to be clear, you're asking a different question now. 10:24:24 10:24:27

Q. I'm not trying to. Again, the assumption is there's -- I'm trying to ask about viscosity and a 29-gauge needle. That's what the question is about. 10:24:29 10:24:31 10:24:33 10:24:36

And the question is, that's a fixed part of the delivery, and the question is, from a formulator's perspective, does it matter whether that delivery is now intravitreal or subcutaneous? 10:24:39 10:24:45 10:24:48 10:24:50 10:24:53

MS. KAYALI: Objection. Vague. Asked and answered, and lacks foundation. 10:24:57 10:24:58

A. As I mentioned, I think the answer is yes. I can explain further, if you want, but I would say yes, it makes a difference. 10:25:07 10:25:11 10:25:14

BY MR. KANE: 10:25:17

Q. Please explain. 10:25:17

A. Okay. The skilled person, as we talked earlier, in the definition of a person of ordinary skill in the art, would work with clinicians, for example, understand the 10:25:18 10:25:26 10:25:32 10:25:36

patient experience, which certainly includes the experience of the clinician, understand some of the issues -- and I discuss some of these in my report, we can go to that. And certainly subcutaneous injection has different aspects than intravitreal injection. 10:25:39 10:25:43 10:25:45 10:25:48 10:25:53 10:26:01

Again, it's your hypothetical. You defined the bore size. I don't think that's realistic, particularly for intravitreal injection, as I understand. 10:26:04 10:26:06 10:26:09 10:26:11

But the skilled person would talk about the experience of the patients and the clinician with the clinical people. And from my experience in those types of discussions, and I actually think it's -- we all can understand this without talking to a clinician, as unpleasant as subcutaneous injection is, intravitreal injection is less pleasant for a patient. So there's potentially more tolerance for length of injection, for pain, for various reactions, swelling, redness, these sort of things for 10:26:13 10:26:16 10:26:20 10:26:23 10:26:28 10:26:32 10:26:34 10:26:40 10:26:44 10:26:48 10:26:53 10:26:59

subcutaneous injection versus intravitreal injection. 10:27:03 10:27:06

And so these are the kind of things -- again, I'm just talking high level from experience, but these are the kind of things that the formulation scientist would engage with the clinician to try to address those concerns, and it really depends on the particular application. 10:27:07 10:27:09 10:27:11 10:27:13 10:27:16 10:27:19 10:27:21

BY MR. KANE: 10:27:24

Q. Okay. Why is viscosity a concern in an intravitreal injection from a formulator's perspective? 10:27:24 10:27:28 10:27:32

A. So I have a whole section on this starting on page 45 in my background. It's "Intravitreal Administration," and then a couple of pages later is a whole section on "Viscosity." And I talk about how it can affect various aspects of the formulation. 10:28:03 10:28:07 10:28:13 10:28:15 10:28:17 10:28:23

And the top of page 52 -- well, actually 51 to 52, I explicitly compare subcutaneous with intravitreal injection, and 10:28:29 10:28:31 10:28:37

I talk about, at the bottom of that top paragraph on page 52, the bottom of Paragraph 93, the issue of the high shear forces through a small needle bore, and so that can affect aggregation, as we've discussed, potentially other routes. 10:28:45 10:28:49 10:28:53 10:28:56 10:29:02 10:29:07

It can affect injection time, which -- I mean, I have a quote here in the parentheses before that specifically about viscosity. Again, viscosity is a measure of the thickness of the solution. If it's very hard for the physician to inject the formulation, intravitreal is one of the most sensitive is my understanding, a needle in their eye, we don't really like that. That causes a lot of discomfort, and so one wants to minimize that. One wants to certainly be wary of, I mean, a not good situation in which a needle could actually be broken off of the syringe. So those are a couple of the examples, and I discuss it more extensively in the section and really throughout my report. 10:29:10 10:29:16 10:29:20 10:29:27 10:29:30 10:29:33 10:29:40 10:29:42 10:29:47 10:29:49 10:29:53 10:30:00 10:30:02 10:30:05 10:30:07 10:30:10

Q. Let's look at that last sentence there. Paragraph 93, it talks about the high shear forces in the small bore needle. 10:30:13 10:30:14 10:30:21

Do you see that? 10:30:25

A. Yes. 10:30:28

Q. Do the shear forces change whether it's an intravitreal injection or a subcutaneous injection? 10:30:30 10:30:32 10:30:36

MS. KAYALI: Objection. Foundation. Vague. 10:30:45 10:30:47

A. I think what you're asking about, the shear forces involved in a given bore needle, and the shear force is going to be a measure of the needle thickness, potentially the materials in the needle itself and also the rate of injection. And all those things can be different for subcutaneous versus intravitreal. 10:30:53 10:30:55 10:31:00 10:31:02 10:31:08 10:31:14 10:31:19 10:31:22

Again, I think the skilled person would take into account the differences in thinking about formulation. 10:31:23 10:31:24 10:31:28

BY MR. KANE: 10:31:31

Q. Well, so back to my -- back to my example. 10:31:31 10:31:33

It's the exact same formulation. It's going to be delivered through a 29-gauge needle. Are the shear forces inside the needle different for intravitreal versus subcutaneous? 10:31:34 10:31:38 10:31:40 10:31:45 10:31:49

MS. KAYALI: Objection. Vague. Foundation. 10:31:50 10:31:53

A. Just so I have your hypothetical, it's the same exact needle with the same bore size? 10:31:56 10:31:57 10:32:02

BY MR. KANE: 10:32:02

Q. Correct. 10:32:02

A. It might be because, as I -- as I just stated in my previous answer, injection time is another factor. And depending on the difference in injection time and the patient tolerance, again, this -- I would get input from a clinician on that, and that affects shear forces too. 10:32:06 10:32:10 10:32:15 10:32:20 10:32:26 10:32:29 10:32:32

Q. How does injection time impact shear 10:32:33

forces? 10:32:37

A. So these -- these formulations can be 10:32:43
Newtonian or non-Newtonian. Newtonian means 10:32:51
that there's a linear response to the shear 10:32:56
force based on the rate, the shear flow. 10:33:00

Remember, viscosity is a dynamic 10:33:03
variable. And so it has seconds in it instead 10:33:08
of poise; the different units have seconds in 10:33:15
it. And so even for a Newtonian-type fluid, 10:33:19
there can be a response which is typically 10:33:25
linear with respect to time. So the shear 10:33:28
forces would be linear with respect to the 10:33:31
rate. 10:33:33

For non-Newtonian fluids, it's 10:33:34
nonlinear, so there's not a proportionality. 10:33:37
So you wouldn't know ahead of time whether a 10:33:41
particular formulation is Newtonian or 10:33:44
non-Newtonian. And whether it's Newtonian or 10:33:46
non-Newtonian can also actually depend on the 10:33:49
rate of flow, in other words, the rate of 10:33:53
injection, because it can be Newtonian under a 10:33:58
certain regime of flow and non-Newtonian under 10:34:01

another regime of flow. 10:34:03

Q. What is your understanding as to the rate of flow difference between intravitreal and subcutaneous injections? 10:34:05 10:34:14 10:34:17

A. I mean, I can tell you my high-level understanding. This is the kind of thing I would consult with a clinician, so I would leave it to the clinician in the particular application. 10:34:25 10:34:28 10:34:30 10:34:35 10:34:39

But as my understanding, from the patient experience, as we've been discussing, one wants to have a -- time is a concern for both, time of injection, but it would be a more significant concern for intravitreal injection versus subcutaneous. I think having a needle in one's eye versus in one's skin, one, you know, relatively would want to have that in for less time. But again, that's my understanding sitting here. I would defer to a clinician who would give me input in that. 10:34:40 10:34:42 10:34:45 10:34:50 10:34:56 10:34:59 10:35:02 10:35:06 10:35:08 10:35:12 10:35:15

Q. Well, I mean, I think you -- it seemed like, and correct me if I'm wrong, you're 10:35:21 10:35:22

mixing time and rate in your answers here. 10:35:24

Because you understand that the 10:35:30

injection intravitreal is far smaller volume 10:35:31

than a typical subcutaneous injection, 10:35:33

right? 10:35:39

MS. KAYALI: Objection. 10:35:40

Foundation. Vague. 10:35:40

BY MR. KANE: 10:35:44

Q. You understand the intravitreal 10:35:44

injections are between 50 and 100 10:35:45

microliters? 10:35:48

A. Yes. I -- I think I discuss that in 10:35:51

my report. 10:35:55

Q. And -- 10:35:55

A. Just I think I -- we can find it, but 10:35:56

I think I say something like "with an emphasis 10:35:58

on 50." 10:36:00

Q. Agree. You understand that 10:36:02

subcutaneous injections are often on the order 10:36:05

of 1 milliliter? 10:36:07

MS. KAYALI: Objection. 10:36:11

Foundation. 10:36:12

A. I think it can be less in circumstances, depending on potency; but yes, I've certainly worked with a lot of formulations that are on the order of 1 milliliter of volume. 10:36:12 10:36:15 10:36:22 10:36:23 10:36:26

BY MR. KANE: 10:36:27

Q. And that's significantly higher than 50 microliters? 10:36:27 10:36:28

MS. KAYALI: Objection. Vague. 10:36:31

A. I mean, it depends on the application. Certainly for an intravitreal application, it's certainly significantly higher. 10:36:32 10:36:39 10:36:43

Again, as we said, one would not want to go over, as I understand from Dr. Bressler, over 100, and one would aim more towards 50, which is, of course, 1/20 of 1 milliliter. 10:36:45 10:36:49 10:36:51 10:36:57

BY MR. KANE: 10:37:01

Q. That's all I'm asking. It's 1/20. So the same rate of injection, subcutaneous and intravitreal, it would take 1/20 of the time intravitreal, right? 10:37:01 10:37:04 10:37:08 10:37:11

MS. KAYALI: Objection. 10:37:12

Foundation. 10:37:13

A. Well, I -- you could have a lower volume subcutaneous. But I would just say if you're -- 10:37:18 10:37:23 10:37:26

BY MR. KANE: 10:37:27

Q. I understand but -- 10:37:27

MS. KAYALI: Sorry, counsel. I would ask you to allow the witness to finish his answer. 10:37:28 10:37:28 10:37:30

BY MR. KANE: 10:37:31

Q. Go ahead. 10:37:31

A. I mean, you're right. If you have the same rate, meaning volumetric flow, yes, it would be a factor of 20 per 1 mL versus 50 microliters. 10:37:31 10:37:34 10:37:40 10:37:47

Q. And I just was making the point that you were -- my perception, maybe you weren't doing -- well, the perception was, you were switching from rate with respect to the shear force analysis to time of the injection and that those are two different parameters, would you agree? 10:37:49 10:37:51 10:37:52 10:37:54 10:38:00 10:38:07 10:38:11

MS. KAYALI: Objection. Foundation. Vague. 10:38:12 10:38:13

A. Rate of injection is different from time of injection. And I believe we can go back and clarify, but that I did not confound the two in my answers to you. 10:38:17 10:38:20 10:38:25 10:38:28

BY MR. KANE: 10:38:31

Q. Well, you were saying that because it was subcutaneous versus intravitreal, you would want the time of the injection intravitreal to be much shorter, and that might affect the -- as I understood your answer, that would, therefore, impact the rate of flow and, therefore, impact the shear forces. 10:38:31 10:38:35 10:38:38 10:38:42 10:38:45 10:38:47 10:38:50 10:38:54

MS. KAYALI: Objection. Foundation. 10:38:55 10:38:56

A. I think what I was saying is that the rate of flow through a given needle with a given bore size and a given material will -- well, sorry, the shear will be affected by the rate of flow. It can be volumetric or linear 10:39:04 10:39:07 10:39:11 10:39:16 10:39:19

because the cross-section in your hypothetical is the same. That's what I was focusing on. The time of injection, I think you call it another parameter, maybe I would say just another aspect for consideration, certainly. But maybe I should add, I mean, from my understanding, again, we can clarify, this would be an input from a medical doctor. 10:39:23 10:39:25 10:39:31 10:39:34 10:39:37 10:39:45 10:39:48 10:39:51

I mean, there's the force on the syringe and things like that, and all of these answers are under your hypothetical, which I said I don't think is the way a skilled person would approach formulation. 10:39:55 10:39:59 10:40:01 10:40:02 10:40:05

BY MR. KANE: 10:40:10

Q. I'm just trying to understand the -- well, I'm trying to understand how a skilled person would approach formulation. 10:40:14 10:40:15 10:40:21

Again, what I'm really just trying to understand, Doctor, is -- and I think you just said here that the shear forces at least are impacted by the rate of flow through a given needle with a given bore size and a given 10:40:23 10:40:24 10:40:29 10:40:32 10:40:38

material, correct? 10:40:40

A. Repeat that just so I make sure I have it. 10:40:46 10:40:48

Q. You said, "I think what I was saying is that the rate of flow through a given needle with a given bore size and a given material," you say, "well, sorry. The shear will be affected by the rate of flow." 10:40:49 10:40:51 10:40:53 10:40:55 10:41:00

A. Yes. 10:41:02

Q. Okay. 10:41:05

A. That's correct. 10:41:05

Q. And will the shear change, if it's an intravitreal delivery -- administration, with all of those things being the same, versus subcutaneous administration, will the shear change? 10:41:09 10:41:11 10:41:15 10:41:18 10:41:21

MS. KAYALI: Objection. Foundation. Vague. 10:41:22 10:41:28

A. As I said, the shear -- the shear will not be different depending on -- well, I guess there -- I should qualify that. I wasn't even taking into account the potential resistance 10:41:29 10:41:37 10:41:39 10:41:44

of the fluid. So I guess that could be a factor on the other side. I was thinking about with your comparison, sort of, syringes just on their own. But there could be varying resistance on the other side which could affect -- which could affect probably more the force, but I was thinking of your hypothetical as sort of an abstract syringe in which case, there's no -- the pressure difference is the same. And if the pressure difference is not the same for intravitreal and subcutaneous, that could have an effect if the fluid is non-Newtonian, the fluid going through the syringe. 10:41:46 10:41:48 10:41:50 10:41:55 10:42:00 10:42:03 10:42:05 10:42:09 10:42:14 10:42:16 10:42:20 10:42:25 10:42:28 10:42:31

But under that sort of abstraction, as I was saying, with no pressure -- the pressure difference being the same, then the shear, with all those other factors the same, will depend on just the rate of flow. I agree with that point. 10:42:35 10:42:38 10:42:41 10:42:46 10:42:49 10:42:53

BY MR. KANE: 10:42:55

Q. Okay. 10:42:55

A. This is all under your hypothetical, though, which I'd emphasize I don't think is realistic for how the skilled formulator would approach a given formulation project. 10:42:55 10:42:56 10:42:59 10:43:03

Q. But is it your testimony that a skilled formulator approaching an invitreal [sic] injection formulation project would be interested in viscosity? 10:43:07 10:43:08 10:43:12 10:43:15

A. I don't mean to be -- I think you -- I thought I heard "invitreal." I think you mean "intravitreal." 10:43:24 10:43:27 10:43:31

Q. Yes. 10:43:31

A. That's what I understood you to mean. Just clarifying, I know that was the -- 99 percent sure that was the case. 10:43:32 10:43:34 10:43:39

I think, as I -- as I said before, the skilled person would take into account viscosity for a given project. You're asking a very high level, to the extent that the skilled person would deem it necessary. And, as I said, certainly for smaller bore needles, viscosity would be more of a potential concern 10:43:43 10:43:48 10:43:51 10:43:53 10:43:57 10:44:02 10:44:05

than for larger bore needles. 10:44:08

Q. And so intravitreal injections use 10:44:14

small-bore needles, correct? 10:44:19

A. That's how I'm characterizing 30 gauge 10:44:23

and smaller. 10:44:26

Q. Yes. 10:44:27

A. Correct. 10:44:27

Q. So in that circumstance, then the 10:44:29

viscosity would be a potential concern for a 10:44:32

formulator? 10:44:36

MS. KAYALI: Objection. Vague. 10:44:38

A. Yes. Again, as of 2018, I think the 10:44:47

skilled formulator would think about viscosity 10:44:50

and whether that -- I mean, as a potential 10:44:55

concern, whether that might be a concern or 10:44:58

not. 10:45:00

BY MR. KANE: 10:45:09

Q. How would a skilled formulator go 10:45:09

about determining viscosity of the 10:45:11

formulation? 10:45:14

A. I mean, there are different methods 10:45:22

that one -- again, we're talking 2018, I'm 10:45:24

presuming. 10:45:29

Q. Yes. 10:45:29

A. Because, I mean, there are various microfluidic methods that were available as of 2018, so one has to measure the viscosity. There are different ways of doing that. 10:45:29 10:45:34 10:45:38 10:45:44

Generally, in development one doesn't have a huge amount of material. So there are microfluidic methods, equipment that one could buy to measure the viscosity, which again, can be a -- a function of the flow rate if it's non-Newtonian. I think -- it's nonlinear. That's what I -- as I explained earlier. 10:45:47 10:45:49 10:45:55 10:46:00 10:46:05 10:46:08 10:46:13

Q. What's your -- 10:46:17

A. I can -- apologies. I paused. I just said I could go into more detail. I didn't think you wanted specifics of the actual measurement. That's why I said a microfluidic device. But if you want more specifics, I could certainly drill down into that. 10:46:18 10:46:20 10:46:22 10:46:25 10:46:27 10:46:30

Q. No. So the -- well, so there are commercially available devices for measuring 10:46:33 10:46:37

viscosities of these protein formulations we've been discussing? 10:46:41 10:46:43

A. Yes. 10:46:48

Q. And just at a high level, how would a -- the skilled formulator use one of those commercial devices? 10:46:51 10:47:00 10:47:04

A. And again, I think we're talking about 2018. That's what I'm understanding -- 10:47:06 10:47:09

Q. Correct. 10:47:12

A. -- because these devices weren't around forever. 10:47:12 10:47:15

At a high level, one would inject the sample. These are microfluidic devices, so there's flow throughout the equipment. And then the difference in -- so flow is caused by difference in pressure. Viscosity is resistance to that flow for difference in pressure. It would be calibrated to viscosities for known materials, fluids. 10:47:18 10:47:20 10:47:24 10:47:31 10:47:35 10:47:38 10:47:41 10:47:45

And so there's pressure -- so the flow rate versus pressure differences could be measured. That's one way of doing it. There 10:47:53 10:47:55 10:47:58

are different -- different approaches, different configurations. 10:48:01 10:48:03

There's -- we've even used, if you have a lot of material, a macroscopic capillary method; but that would be, I think, what would generally be used in a -- in a, you know, fairly sophisticated pharmaceutical development laboratory in 2018. 10:48:07 10:48:09 10:48:11 10:48:16 10:48:22 10:48:25

Q. Do you have those kinds of machines in your laboratory? 10:48:27 10:48:30

A. I have viscometers, but they're more the macroscopic ones. I've used the more micro viscometers with collaborators who have had them at companies, so I don't have one of those in my lab. 10:48:32 10:48:36 10:48:41 10:48:44 10:48:47

Q. How does the viscometer work that you have in your lab? 10:48:48 10:48:52

A. Oh, I was just talking about a standard viscometer, which is typically a glass, and you can -- you put the fluid in the glass, and then you measure how the fluid -- it's -- it's easier to describe with a 10:48:55 10:48:57 10:49:02 10:49:05 10:49:08

picture. But it generally has a bulb so you can measure how the flow is in that viscometer and get -- and again, it's -- it has to be calibrated. It comes precalibrated to viscosities of known fluids. And so how the fluid balances in the -- it kind of has a U-shape with a bulb. That gives you a measure of the viscosity. 10:49:12 10:49:15 10:49:18 10:49:20 10:49:27 10:49:32 10:49:35 10:49:37

I don't think that would typically -- we can do that because we can get a lot or generate a lot of product. That is sort of the traditional one, maybe been around for many, many decades. I think as of 2018, it's a big issue with lack of materials, sample materials. And so I think that most labs would use the more micro viscometers that I mentioned, but that's what we've used in our lab for a variety of applications. 10:49:40 10:49:42 10:49:45 10:49:47 10:49:52 10:49:55 10:50:00 10:50:03 10:50:07 10:50:09

Q. And both approaches would give you the same viscosity reading? 10:50:12 10:50:13

MS. KAYALI: Objection. Foundation. 10:50:17 10:50:17

A. Well, that -- that is an important question, because again, the viscosity can depend on the pressure difference. 10:50:19 10:50:23 10:50:27

In these more macroscopic ones that I have that we've used when you have a lot of material, have a much larger size diameter for flow. It's a cross-section for flow. 10:50:34 10:50:37 10:50:40 10:50:47

So if it's Newtonian, it will give you the same number. But if it's non-Newtonian, again, there's a nonlinear effect, the numbers can be -- can differ. That's why these viscometers give you a measure of the viscosity per se, but then the actual application from, like, a medical professional at the end of the day is what's important. So there can be differences. You know, there's a summary answer for the reasons I mentioned. 10:50:52 10:50:55 10:51:01 10:51:04 10:51:09 10:51:12 10:51:15 10:51:19 10:51:22 10:51:23 10:51:26

BY MR. KANE: 10:51:27

Q. When you say "the actual application for the medical professional," could you explain what you mean by that? 10:51:27 10:51:39 10:51:43

A. Of course.

You asked about whether these different types of methodologies, and they're quite different in the sense that one is sort of -- the one that we've used is sort of a basic laboratory method that's been around for a long, long time, which presumes one has a lot of fluid material.

The micro viscometers, I think the one that would generally be used for formulation applications in 2018 if viscosity were an issue to be studied, have different dimensions, much smaller dimensions in terms of the tubing and whatnot that the fluid would go through. And if the fluid is what I'm calling non-Newtonian, that's the term which means there's not a linear or directly linear response, the values can be different.

And so at the end -- the ultimate measure of the effect of viscosity, let's say, a laboratory viscosity versus a target is, does it do what it's supposed to do when it's

actually used therapeutically. 10:53:05

So we've even -- we even developed a little method where you can actually test flow through a syringe per se as opposed to these other different viscometers to try to get a sense of how the viscosity per se can be related to flow through a syringe. So it's not -- it doesn't necessarily correspond perfectly, but when you attempt to correlate the two, so if one is worried about viscosity, to have a target viscosity for a given application. 10:53:08 10:53:13 10:53:15 10:53:17 10:53:22 10:53:25 10:53:28 10:53:30 10:53:35 10:53:39 10:53:41

BY MR. KANE: 10:53:47

Q. There's been -- in the patents -- we'll get to those at some point -- there is some viscosity testing that was conducted. You saw that, correct? 10:53:47 10:53:50 10:53:52 10:53:56

A. Yes. 10:54:00

Q. And so based on that, do you have an understanding whether the viscosity of those formulations was Newtonian or non-Newtonian, or the behavior of those formulations was 10:54:03 10:54:04 10:54:07 10:54:11

Newtonian or non-Newtonian? 10:54:13

MS. KAYALI: Objection. Vague. 10:54:16

A. I think if we're going to start 10:54:17

talking about the patents and the data in the 10:54:20

patent, we should maybe look at it. You said 10:54:22

we'd get to it, but maybe this is a time -- 10:54:25

BY MR. KANE: 10:54:26

Q. Are you sure that you -- we'll get to 10:54:26

it, but I just was -- if you have a 10:54:29

recollection as to -- or an understanding as 10:54:30

to whether it was Newtonian or non-Newtonian. 10:54:32

MS. KAYALI: Objection. Vague. 10:54:37

Foundation. 10:54:38

A. I'd want to look at the patent. I 10:54:38

guess I could look at my -- the data that I 10:54:40

have in my report, but we may as well just -- 10:54:43

Q. Okay. We'll just move on. 10:54:45

A. Oh, okay. 10:54:47

Q. We'll get back to it. 10:54:47

A. Okay. 10:54:48

Q. So we've been talking about 10:55:47

intravitreal injections, and you would agree 10:55:49

that by 2018, intravitreal therapeutic protein formulations were known in the field? 10:55:53 10:55:59

A. There certainly were products before 2018 that were administered intravitreally. 10:56:11 10:56:12

Q. And a skilled formulator wanting or looking to formulate an intravitreal product could go into the literature and find excipients or additives that have been used in intravitreal administration before 2018? 10:56:20 10:56:22 10:56:28 10:56:31 10:56:36

A. Yes, there were excipients that had been used before, that I guess the skilled formulator would be able to find those, most or all of them, at least in the U.S., I would think. 10:56:44 10:56:46 10:56:50 10:56:54 10:56:58

Q. So, Dr. Trout, if you look at Paragraph 89 of your... 10:57:29 10:57:30

A. Okay, I'm there. 10:57:41

Q. You cite the Chang 2002 reference. 10:57:42

Do you see that? 10:57:50

A. Yes. 10:57:56

Q. And Chang 2002 teaches that "It's preferable to use excipients with similar 10:58:01 10:58:04

frequency of dosing, history of chronic use, and similar patient populations to ensure safety approval." 10:58:05 10:58:09 10:58:14

Do you see that? 10:58:15

A. Yeah. Again, just to -- since we're reading it, it says, "to ensure approval and safety." I think you reversed them, but I don't think that makes a difference. 10:58:15 10:58:20 10:58:23 10:58:26

Q. Okay. So you agree with that statement from Dr. Chang? 10:58:30 10:58:31

MS. KAYALI: Objection. Foundation. 10:58:35 10:58:37

A. I agree with that statement, as long as it's understood in the context. It's preferable, and certainly as I emphasize, there are many, many exceptions. It's -- if anything is a rule, it's a rule of thumb, not a hard fast rule, but as it's stated, it's preferable, yes, I agree. 10:58:40 10:58:42 10:58:47 10:58:51 10:58:54 10:58:57 10:59:00

BY MR. KANE: 10:59:09

Q. Okay. And by 2018, aflibercept was known in the art, correct? 10:59:09 10:59:15

A. Yes. You're asking about the molecule aflibercept, yes. 10:59:20 10:59:21

Q. Yes. And Regeneron started working with aflibercept in approximately 2002 or 2003. Do you recall that? 10:59:23 10:59:30 10:59:34

MS. KAYALI: Objection. Foundation. 10:59:37 10:59:39

A. Since this is a factual question, is there a place in my report? I could try to look. 10:59:39 10:59:43 10:59:45

BY MR. KANE: 10:59:45

Q. I don't think it's in your report. 10:59:45

A. Oh. 10:59:47

Q. I'm just asking if you have any recollection of when Regeneron started working with aflibercept. 10:59:47 10:59:48 10:59:50

A. (Witness reviews document.) 10:59:54

I just -- I've got the section on fusion proteins in which I certainly discuss aflibercept in Paragraph 78. Well, obviously throughout the report. 11:00:22 11:00:25 11:00:29 11:00:35

I just don't remember internally. I 11:00:39

mean, if that's what you tell me, it sounds like a realistic time frame. I suppose that can be confirmed. 11:00:42 11:00:45 11:00:47

Q. Okay. So by -- well, if you look at your report again, just to sort of give you some road or some landmarks, if you look at Paragraph 59, do you see that relates to the Furfine patent that we'll be talking about? 11:00:55 11:01:01 11:01:03 11:01:09 11:01:18

A. Yes, this section, yes. 11:01:23

Q. And the Furfine patent includes information about aflibercept, correct? 11:01:25 11:01:32

A. Yes, I guess, certainly as I discuss at a high level, yes, that's fair. 11:01:44 11:01:49

Q. And you see that it issued October 27, 2009, the first line? 11:01:50 11:01:52

A. Yes. 11:01:59

Q. And it was -- and you would understand that it would be filed sometime before 2009 then? 11:02:01 11:02:02 11:02:04

MS. KAYALI: Objection. Foundation. 11:02:06 11:02:07

A. Again, that's -- you're the attorney, 11:02:11

but that sounds reasonable. That's my understanding. 11:02:14 11:02:16

BY MR. KANE: 11:02:18

Q. Okay. So by 2018, Regeneron had been working with aflibercept for more than a decade, correct? 11:02:18 11:02:21 11:02:23

A. I'm not sure how they would say it, but certainly, before 2009 to 2018 is -- I guess, as long as it's before 2008, that's more than a decade. That sounds -- the math is right. 11:02:36 11:02:38 11:02:45 11:02:48 11:02:50

Q. Okay. And they had actually had the original Eylea formulation approved before 2018, correct? 11:02:51 11:02:53 11:03:00

A. That's my understanding. I mean, I guess they just called it Eylea, but yes, that's my understanding. 11:03:01 11:03:03 11:03:08

Q. Right. So Regeneron had significant experience working with aflibercept by 2018? 11:03:09 11:03:14

A. I guess that's fair. I'm not -- sounds like a relative term, relative to what, but certainly I would think Regeneron has had 11:03:22 11:03:24 11:03:27

a lot of experience. If you call it significant... 11:03:31 11:03:34

Q. Okay. If you had questions or wanted to learn more about aflibercept, do you think Regeneron's scientists would be a good place to seek information? 11:03:36 11:03:38 11:03:40 11:03:44

MS. KAYALI: Objection. Vague. Foundation. 11:03:50 11:03:51

A. If I wanted to learn? I don't know. Maybe I -- I would perhaps look at what's public and do research in my lab. It depends on what I wanted to learn and how and why. 11:03:57 11:04:00 11:04:08 11:04:12

BY MR. KANE: 11:04:16

Q. Okay. But you wouldn't consider asking people that had been working with the molecule for more than ten years about their -- the attributes of their molecule? 11:04:16 11:04:19 11:04:22 11:04:25

MS. KAYALI: Objection. Foundation. Incomplete hypothetical. 11:04:29 11:04:30

A. I mean, you're asking a very high-level question. I've done work on a lot of biologics, and I didn't talk to the company 11:04:36 11:04:38 11:04:43

who marketed them in my laboratory at MIT. It just really depends on what I'm trying to do. 11:04:46 11:04:50

BY MR. KANE: 11:04:54

Q. Would you look at patents and publications about aflibercept from Regeneron? 11:04:54 11:04:55

A. I'm -- again, when you say me, I'm presuming you mean me as an MIT scientist in my laboratory, yes. 11:05:02 11:05:08 11:05:11

So, okay, yes, as you say. 11:05:14

So, you know, generally, in my work at MIT, we focus on published literature. I'm not sure if we would -- I would look at patents. I would be interested in published literature, depending -- which might depend on what I'm trying to do. 11:05:20 11:05:23 11:05:30 11:05:32 11:05:36 11:05:39

Q. If you look at Paragraph 78 of your declaration. 11:05:59 11:06:01

A. Okay, I am there. 11:06:12

Q. You see there that aflibercept was approved by the FDA for use in 2011? 11:06:14 11:06:17

A. Yes. 11:06:29

Q. And is it your understanding that 11:06:35

Eylea low dose is a stable liquid formulation of aflibercept? 11:06:37 11:06:41

MS. KAYALI: Objection. 11:06:46

Vague. 11:06:49

A. I mean, I think we talked about this earlier. If you mean the Eylea that's mentioned here in Paragraph 78, I'm referring to Exhibit 2064, I would say that it went through the FDA approval process. So the FDA thought that, in terms of stability, it was -- it met the threshold of safe and effective. 11:06:49 11:06:53 11:06:56 11:07:03 11:07:08 11:07:13 11:07:16

BY MR. KANE: 11:07:37

Q. By 2018, the structure of aflibercept was known in the art? 11:07:37 11:07:40

A. Well, let's be clear. Just to be clear, what do you mean by "structure"? Do you mean the primary structure? Or is there a place in my report? 11:07:49 11:07:53 11:07:56 11:08:03

Q. In Paragraph 303, this is the -- talking about the buffering. 11:08:06 11:08:12

A. Okay, I am there. 11:08:29

Q. The first sentence, "Based on the 11:08:47

known structure of VEGF receptor fusion proteins like aflibercept, the POSA would understand that such proteins could also have buffering capacity," correct? 11:08:49 11:08:52 11:08:56 11:08:58

A. Yes, understood, but -- yes, and I -- that's why I asked you about the primary structure, if that's what you had in mind, because I reproduced that in subsequent page 233. 11:09:02 11:09:08 11:09:12 11:09:14 11:09:17

Q. Okay. 11:09:20

A. So yes. 11:09:20

Q. Okay. Have you -- you haven't in your report identified any references or data suggesting that aflibercept had shown aggregation issues? 11:09:21 11:09:40 11:09:43 11:09:49

A. Well, what do you mean by "aggregation issues"? 11:09:58 11:10:03

Q. Problems with aggregation leading to instability. 11:10:05 11:10:08

A. Like, leading to, like, issues with the product, a recall with the product? Or what do you mean by "issue"? What do you mean 11:10:12 11:10:17 11:10:20

by "issue"? 11:10:22

Q. Well, I'm just asking if you've identified any references suggesting that aflibercept had aggregation issues? 11:10:23 11:10:24 11:10:28

MS. KAYALI: Objection. Vague. 11:10:31 11:10:32

A. I understood the first part. I'm just trying to get clarity on what you mean by "issues." Like a -- product issues? Or process? I mean, something that led to -- 11:10:37 11:10:39 11:10:43 11:10:46

BY MR. KANE: 11:10:53

Q. Any of those. 11:10:53

MS. KAYALI: Objection. Vague. 11:10:54

A. I mean, I have a whole variety of references here. I don't know if I can, on the fly, prove a negative. Frankly, I'm not quite sure what you're asking. 11:10:54 11:11:35 11:11:39 11:11:44

I mean, proteins in general are susceptible to aggregation, and so that has to be addressed. And we went through how the process typically works, as I understand it. 11:11:49 11:11:52 11:11:56 11:11:59

We'd have to -- unless there's something 11:12:03

specific you have in mind. 11:12:06

BY MR. KANE: 11:12:10

Q. Do you have an understanding as to whether aflibercept is more susceptible to aggregation than monoclonal antibodies? 11:12:10 11:12:11 11:12:16

MS. KAYALI: Objection. Foundation. Vague. 11:12:19 11:12:20

A. I mean, clearly, it depends on the specifics. But as I say, for example, in Paragraph 76, on page 39 at the top, "Unlike antibodies, fusion proteins are not naturally occurring structures and have not evolved to possess features that confer stability." 11:13:00 11:13:04 11:13:08 11:13:15 11:13:18 11:13:20

So I think the -- as I've said, I mean, just at a high level, there'd be a concern from the skilled person for fusion proteins over antibodies just in general in terms of being more susceptible to degradation processes, including aggregation, which is, I think, what you asked. 11:13:25 11:13:29 11:13:33 11:13:37 11:13:41 11:13:45 11:13:47

BY MR. KANE: 11:13:51

Q. But you don't cite any data supporting 11:13:51

the conclusion that aflibercept is more susceptible to aggregation than monoclonal antibodies, correct? 11:13:54 11:13:56 11:13:59

MS. KAYALI: Objection. Foundation. 11:14:00 11:14:02

A. Again, I'm happy to -- you're asking me about a negative. I -- there's a lot of references. 11:14:10 11:14:12 11:14:15

BY MR. KANE: 11:14:16

Q. Well, I'm asking in this paragraph, do you cite any data? 11:14:16 11:14:17

MS. KAYALI: Sorry. Dr. Trout, were you finished with your answer? 11:14:18 11:14:19

Please don't interrupt the witness. 11:14:21

THE WITNESS: No. 11:14:24

A. I was saying that -- I mean, I have a lot of references here. You're asking me to state a negative. I'd want to go through. It would probably take some time to be able to answer that. 11:14:24 11:14:26 11:14:31 11:14:35 11:14:38

Here I'm giving just a general approach based on the reasoning that I state 11:14:39 11:14:41

here. It's just a general understanding. 11:14:45

BY MR. KANE: 11:15:06

Q. Do you have an understanding as to whether aflibercept is more difficult to formulate as compared to monoclonal antibodies? 11:15:06 11:15:20 11:15:23 11:15:25

MS. KAYALI: Objection. Vague. 11:15:28

A. I mean, you're asking me to compare formulation of a specific -- the formulation process of a specific molecule with that of a category. 11:15:29 11:15:41 11:15:43 11:15:48

My understanding, as I've expressed, is that there's a lot of -- it depends on some antibodies are more difficult than others to formulate. I was just talking about just a high level, one could potentially do a comparison, maybe based on the references here, but my simple point is that antibodies have evolved. I think we're all familiar with antibodies in our bodies, to confer stability. 11:15:51 11:15:54 11:16:00 11:16:03 11:16:08 11:16:14 11:16:16 11:16:21 11:16:26

These monoclonals are typically made antibodies, but they have a lot of the 11:16:31 11:16:33

structure that's similar. 11:16:35

Eylea, as I -- or aflibercept, as I 11:16:38

point out at the very bottom, involves fusing 11:16:41

different domains, so it doesn't possess sort 11:16:47

of the overall structure. It's a nonnaturally 11:16:52

occurring protein molecule in terms of its 11:16:57

overall structure. 11:16:59

That's -- that's the point here. 11:17:02

BY MR. KANE: 11:17:32

Q. If you look at Paragraph 90. 11:17:32

A. Okay, I am there. 11:17:42

Q. If we look at the sentence that begins 11:17:49

at the very bottom of the page, "As 11:17:54

concentration." 11:17:56

Do you see that? 11:17:58

A. Yes. 11:18:03

Q. So it was well known by 2018 that as 11:18:04

the viscosity -- excuse me, that as -- 11:18:07

viscosity of a protein solution generally 11:18:09

increases as the concentration increases? 11:18:12

A. I think that would generally be 11:18:21

considered correct. 11:18:24

Q. Okay. 11:18:27

A. I mean, there can be exceptions for reasons, but again, this point is just in general. 11:18:28 11:18:30 11:18:33

Q. And likewise, on Paragraph 95 you say, the first sentence, "The challenges of viscosity in high-concentration protein formulations were well-recognized in the literature prior to the priority date." 11:18:39 11:18:41 11:18:51 11:18:53 11:18:56

Do you see that? 11:19:06

A. Yes. 11:19:06

Q. And I think we looked at earlier, Paragraph 94, by 2018 -- 11:19:30 11:19:33

A. Just one second. 11:19:37

Q. Sorry. 11:19:38

A. Oh, okay. I thought you were quoting something. I'm at the beginning of Paragraph 94. 11:19:41 11:19:44 11:19:47

Q. Okay. We talked about, earlier, that by 2018, there were strategies, including adjusting pH, adding salts or amino acids or optimizing buffer selection to influence 11:19:48 11:19:49 11:19:53 11:19:58

viscosity? 11:20:04

A. Yes, we did, and I think that's 11:20:14

correct, again understanding that, as I 11:20:15

discuss in my report, these are general 11:20:17

strategies, and how they can be successful in 11:20:20

a given product wouldn't have been known 11:20:25

without empirical testing. 11:20:29

Q. And if there wasn't a viscosity issue 11:20:42

with an aflibercept formulation, you agree 11:20:46

that those strategies could be applied to that 11:20:48

formulation subject to empirical testing? 11:20:55

MS. KAYALI: Objection. Vague. 11:21:01

Foundation. 11:21:05

A. I -- I may have misheard you. I guess 11:21:05

I need to speak louder, too. 11:21:08

I thought you said if there's not a 11:21:11

viscosity issue. 11:21:12

BY MR. KANE: 11:21:13

Q. No, I didn't, sorry. 11:21:13

A. Oh. 11:21:15

Q. Or maybe I misspoke. I don't know. 11:21:28

So by 2018, if there was an issue with 11:22:18

an aflibercept formulation, you agree that these strategies could be applied to that formulation, subject to empirical testing? 11:22:26 11:22:31 11:22:36

MS. KAYALI: Objection. Vague. Foundation. 11:22:44 11:22:44

A. I mean, if I understand your hypothetical, I think it would be important to understand what "issue" means. If there's a -- if something arises -- I mean, under your hypothetical, the product is being produced and then all of a sudden there's an issue. 11:22:49 11:22:55 11:22:58 11:23:05 11:23:08 11:23:12

BY MR. KANE: 11:23:16

Q. Poor question. 11:23:16

If a formulator wanted to reduce the viscosity of an aflibercept formulation, these strategies could be employed, subject to empirical testing? 11:23:20 11:23:21 11:23:29 11:23:34

MS. KAYALI: Objection. Vague. 11:23:36

A. I think, broadly speaking, that's correct. I mean, these are -- these are high-level strategies we're talking about, and as I say in the very next sentence, "However, 11:23:36 11:23:44 11:23:48 11:23:52

the prior art recognized that such strategies do not always succeed, and what works for one protein may not work for another due to the protein-specific nature of protein-protein interactions and viscosity behavior." 11:23:55 11:23:58 11:24:02 11:24:05 11:24:09

And I should probably add, I think it's in here somewhere, but interactions between or among the various excipients that are added and the proteins themselves differ. That's why -- these are strategies that have been successful to some degree or another in the past for other proteins, so one attempts to address these -- sorry -- viscosity in your question for a specific protein, and I think the skilled person would understand what I just stated. 11:24:12 11:24:14 11:24:18 11:24:21 11:24:25 11:24:28 11:24:34 11:24:38 11:24:43 11:24:47 11:24:49

MR. KANE: Should we take another break? 11:24:56 11:24:56

THE WITNESS: It's up to you. Do you want to take a break? 11:24:59 11:25:00

MR. KANE: Yes. 11:25:01

THE WITNESS: Okay. Sure. 11:25:01

THE VIDEOGRAPHER: This is the end of Media No. 2. We are going off the record. The time is 11:25 a.m. 11:25:01 11:25:04 11:25:06

11:25:27

(Recess taken from 11:25 a.m. to 11:41 a.m.) 11:25:27 11:25:27

11:25:27

THE VIDEOGRAPHER: This is the beginning of Media No. 3. We are going back on the record. The time is 11:41 a.m. 11:32:24 11:41:05 11:41:08

BY MR. KANE: 11:41:14

Q. Welcome back, Dr. Trout. 11:41:14

A. Thank you. 11:41:16

Q. I'm going to hand you what's been marked as Alvotech 1001, which is the '036 patent. 11:41:16 11:41:19 11:41:25

A. Okay. 11:41:26

MS. KAYALI: Thank you. 11:41:27

BY MR. KANE: 11:41:41

Q. And this is obviously a patent that you have reviewed, correct? 11:41:41 11:41:42

A. (Witness reviews document.) 11:41:48

Yes. 11:41:56

Q. What did the inventors of the '036 patent invent? 11:42:07 11:42:14

MS. KAYALI: Objection. Vague. Calls for a legal conclusion. 11:42:15 11:42:16

A. I mean, they -- I would let the patent speak for itself. It's a pretty extensive document and the abstract summarizes things. 11:42:51 11:43:00 11:43:03

The very first page, number 57, it says, "The present invention provides ophthalmic formulations having high concentrations of vascular endothelial growth factor (VEGF) receptor fusion protein and high stability during storage. Methods for treating angiogenic eye disorders using the high-concentration formulations are also provided." 11:43:09 11:43:13 11:43:15 11:43:17 11:43:20 11:43:26 11:43:28 11:43:32 11:43:35

And then, of course, there are the claims and the specification, but I would -- if you needed a summary, I guess that's -- the abstract would be one. 11:43:38 11:43:39 11:43:41 11:43:44

BY MR. KANE: 11:43:47

Q. Did the inventors identify a problem in the art? 11:43:47 11:43:50

A. (Witness reviews document.) 11:44:37

I mean, I certainly discuss the problem, for example, in my "Objective Evidence Supports Nonobviousness" section starting on page 119. You asked me about the inventors. I mean, there's a whole background, for example, from the inventors, starting in Column 1 going through Column 2, and then there's a summary. 11:44:41 11:44:43 11:44:45 11:44:50 11:44:53 11:45:00 11:45:01 11:45:05

I mean, I guess at the very top, just to excerpt, it says, "There's a need in the art" -- sorry, I should be explicit. I think it's line 1 in Column 2, halfway through. 11:45:07 11:45:11 11:45:14 11:45:18

"There's a need in the art for preparing high concentration, high stability, antibody, and protein formulations which would include the proper potency, stability, viscosity, osmolality, and pH." 11:45:22 11:45:23 11:45:27 11:45:29 11:45:32

It's a high-level statement. And then the next paragraph talks about -- talks about 11:45:36 11:45:37

the VEGF we had been referring to. But, I mean, that's an excerpt. 11:45:40 11:45:43

I would -- the question is sort of high level. I would take the document as a whole of what they -- what the inventors discussed. 11:45:47 11:45:48 11:45:50 11:45:54

Q. You would agree before the filing there was -- 11:46:01 11:46:02

A. Sorry. Do you mind... 11:46:04

Q. Before the filing of the patent, there were stable liquid formulations of aflibercept, correct? 11:46:04 11:46:10 11:46:13

A. I mean, again, if you mean by "stable," suitably stable, I mean, there was Eylea, which we had discussed, certainly before the filing of the patent, as we discussed. So it was stable enough to become a commercial product. 11:46:23 11:46:27 11:46:31 11:46:33 11:46:35 11:46:39

Q. Okay. And this patent relates to concentrations of aflibercept that are greater than the commercial product, correct? 11:46:41 11:46:52 11:46:54

MS. KAYALI: Objection. Vague. 11:46:59

A. I mean, the -- if by "the commercial product" we mean the Eylea, that's, as I recall, I mean, it's in the label. But I think we all know that's formulated at 40 milligrams per milliliter. That's what's in the label, which we recall. And the invention talks about, for example, in Column 3, starting at line 31, it talks about from about 41 milligrams per milliliter, which is above that. It talks about an embodiment of the invention, at the very end of that Paragraph 38 and 39, which comprises about 40 milligrams per milliliter of the VEGF receptor fusion protein. 11:47:00 11:47:30 11:47:33 11:47:36 11:47:38 11:47:41 11:47:46 11:47:49 11:47:55 11:48:02 11:48:06 11:48:09 11:48:14 11:48:16

I mean, if we go to the claims, which I'm sure you'll want to do it at some point, you know, Claim 1 is starts at 100, and there are other claims with concentrations that are above 40, if that's what you mean. 11:48:19 11:48:21 11:48:24 11:48:28 11:48:30

BY MR. KANE: 11:48:33

Q. Yes. Did the inventors of the '036 patent develop some new formulation strategy 11:48:33 11:48:49

for formulating protein formulations? 11:48:56

MS. KAYALI: Objection. 11:49:05

Foundation. Scope. 11:49:06

A. I think the inventors developed a new 11:49:26

formulation strategy that they specifically 11:49:29

applied to aflibercept, and I discuss that 11:49:33

many pages in the report and all the examples 11:49:39

and example formulations and explicit examples 11:49:42

that they use are for aflibercept. 11:49:47

BY MR. KANE: 11:49:52

Q. Okay. What's the new formulation 11:49:52

strategy? Did they use new excipients, for 11:49:55

instance, compared to what's in the 11:50:04

formulator's tool of excipients? 11:50:06

MS. KAYALI: Objection. Vague. 11:50:32

A. (Witness reviews document.) 11:50:36

I mean, it is pretty vague. To the 11:50:37

extent I understand your question, I -- I 11:50:38

mean, I was going to point to a place in my 11:50:43

report, but it's really discussed, I would 11:50:45

say, throughout the report in all the 11:50:48

different sections. 11:50:50

I mean, I talk about page 156 of the report. I just happen to come here, but it's really throughout, as I discuss all the claims. I talk about the dose and the concentration in particular of aflibercept. 11:50:51 11:50:57 11:51:01 11:51:05 11:51:07

These are -- I just happened to go to some of the claims that have a concentration of about 114.3. So I would say what's new is that they were able to apply these high-level approaches that had been developed over the years and able to formulate aflibercept in a way that was not done before to lead to the invention as, for example, in the claims. 11:51:11 11:51:13 11:51:16 11:51:24 11:51:27 11:51:31 11:51:39 11:51:44

And I agree they used excipients that had been known before. I'm kind of answering -- you asked two questions, so I'm kind of answering both. 11:51:48 11:51:50 11:51:53 11:51:56

But that's, as we've talked about, the whole challenge of formulation. There are excipients that have been used before, but can they be used and how can they be used for a particular application is part of the art of 11:51:57 11:51:59 11:52:02 11:52:05 11:52:09

1	the formulation scientist going forward.	11:52:12
2	BY MR. KANE:	11:52:32
3	Q. Did the 'O3 [sic] patent describe some	11:52:32
4	new strategy for reducing the viscosity of	11:52:36
5	high-concentration protein formulations?	11:52:39
6	A. Again, you ask these high-level	11:52:40
7	questions, and the answer is yes, for the	11:52:51
8	aflibercept formulations that are discussed	11:52:56
9	here. The focus of the patent is the	11:52:58
10	aflibercept formulations, and I discuss over	11:53:00
11	30. I mean, there are more -- many more than	11:53:06
12	that, but certainly I enumerate several of	11:53:09
13	those formulations, but they're all	11:53:12
14	aflibercept formulations.	11:53:17
15	Q. But you said, just on the last	11:53:20
16	question, it's applying the same strategy but	11:53:23
17	to aflibercept at these higher	11:53:25
18	concentrations?	11:53:26
19	MS. KAYALI: Objection. Vague.	11:53:29
20	A. I don't think that's what I said. I	11:53:29
21	said that at high level, as we discussed in	11:53:34
22	the background, there are, I'll call them	11:53:40

strategies or approaches to formulate or attempt to formulate proteins that have been developed over the years because they had worked on, whatever the application, to other proteins. 11:53:44 11:53:47 11:53:52 11:53:54 11:53:59

And here the inventors developed, call it a category or strategic approach or whatever, that they were able to apply to aflibercept, which hadn't been done before, and there was no way to predict it. 11:54:01 11:54:05 11:54:08 11:54:11 11:54:14

I mean, if we're talking about obviousness, we can talk about the different criteria that I went through. 11:54:17 11:54:18 11:54:20

BY MR. KANE: 11:54:24

Q. Well -- 11:54:24

MS. KAYALI: Sorry. Dr. Trout, were you finished? 11:54:25 11:54:25

THE WITNESS: Oh, yeah, that's all right. I was finished. Thank you. 11:54:27 11:54:27

BY MR. KANE: 11:54:29

Q. Let's make it clear, though, aflibercept had been formulated into stable 11:54:29 11:54:30

liquid formulations before the '036 patent, correct? 11:54:33 11:54:43

A. I think as I -- I already answered that. I'll try to reproduce my answer. 11:54:43 11:54:45

It had been formulated at 40 mgs per mL in Eylea. And the point about stability is that it was suitably stable to become a commercial product. 11:54:51 11:54:56 11:55:00 11:55:03

Q. Correct. 11:55:05

A. That doesn't mean that it's stable in any conditions. Under the conditions that -- in which it's supposed to be stored and used. 11:55:05 11:55:07 11:55:11

Q. Well, okay. So you read for -- we read at the top, I think, of Column 3, right -- or Column 2, excuse me, it says that, "There's a need in the art for preparing high concentration, high stability antibody and protein formulations that include the proper potency, stability, viscosity, osmolality, and pH," correct? 11:55:14 11:55:22 11:55:24 11:55:43 11:55:45 11:55:50 11:55:53 11:55:58

A. Yes, you read that correctly. 11:56:01

Q. What does "high stability" mean 11:56:05

there? 11:56:07

MS. KAYALI: Objection. 11:56:15

Foundation. 11:56:19

A. I read it, and I think the formulator 11:56:20

would read it to mean that under whatever the 11:56:22

conditions are, that as of 2018, the objective 11:56:29

is to increase the stability. So it's not a 11:56:35

comparative, but to have a high stability 11:56:40

under more stress conditions like higher 11:56:43

concentration. 11:56:48

And this is a high-level statement, 11:56:52

fine. I mean, the inventors are saying that 11:56:53

it has to have a high stability, and I guess 11:56:56

relative to what's been in the past. 11:57:00

BY MR. KANE: 11:57:03

Q. So you think that the formulations in 11:57:03

this patent are higher than the stability of 11:57:05

the Eylea product? 11:57:08

MS. KAYALI: Objection. 11:57:16

Foundation. Vague. 11:57:20

A. I think as we've discussed, the 11:57:23

inventions here are -- have higher 11:57:28

concentration and so are more susceptible to degradation routes. And way back early this morning, I mentioned viscosity is not a degradation per se, but clearly an issue here in this patent and an issue that the formulator would or could address, if needed. And that's what the inventors have addressed here. So it has -- under these higher stress conditions of concentration, it has a high stability, so higher concentration than in the past, with adequate stability and addressing viscosity as is -- as you read correctly and as stated here. 11:57:33 11:57:39 11:57:42 11:57:48 11:57:52 11:57:54 11:58:00 11:58:03 11:58:07 11:58:11 11:58:15 11:58:22 11:58:25

BY MR. KANE: 11:58:27

Q. I'm confused as to when you say "higher stability than in the past," or you say "higher concentration than in the past." 11:58:27 11:58:29 11:58:34

Okay. So you're saying higher concentration than in the past, but not higher stability than in the past, correct? 11:58:40 11:58:43 11:58:44

MS. KAYALI: Objection. Vague. 11:58:49

A. I mean, this is qualitative. I think 11:58:51

what I was saying, clarify, a skilled person would understand that at higher concentrations, there's more driving force for degradation, and so the formulation challenges are increased. 11:58:54 11:59:02 11:59:05 11:59:09 11:59:13

And so I think that's what they're saying, as one tries to get higher concentrations, one needs to have higher stability because the driving forces to degradation are higher. 11:59:16 11:59:17 11:59:21 11:59:22 11:59:25

Again, this is a high-level statement. It's not even specific to aflibercept. But that -- that's how I think the skilled person would understand this statement. And viscosity, too, is an issue as stated here. 11:59:26 11:59:29 11:59:32 11:59:34 11:59:39

BY MR. KANE: 11:59:43

Q. Then my question with that background then is, the inventors used the excipients that had been previously used in pharmaceutical formulations, including Eylea low dose, and applied those excipients and strategies to these higher concentrations of 11:59:43 11:59:46 12:00:11 12:00:13 12:00:16 12:00:22

aflibercept to arrive at this invention; is that fair? 12:00:25 12:00:29

MS. KAYALI: Objection. Foundation. 12:00:34 12:00:36

A. I just want to clarify. What do you mean "including Eylea"? Including the aflibercept? 12:00:36 12:00:37 12:00:40

BY MR. KANE: 12:00:40

Q. Yes. 12:00:40

A. So the -- yes, aflibercept was known before the invention, and the excipients that were employed here were known before the invention. I agree with that point. 12:00:46 12:00:52 12:00:58 12:01:00

Q. Okay. 12:01:03

A. And there are these high-level strategies. The point is that the inventors were able -- I mean, there's so many examples here, and you see, you know, the different combinations and whatnot, the degrees of freedom that the inventors explored to develop the invention here, and this is the art of formulation and developing and inventing new 12:01:04 12:01:06 12:01:09 12:01:13 12:01:15 12:01:19 12:01:23 12:01:30

formulations is to come up with formulations that meet criteria and address this need that we've been discussing. And that -- and no one would have been able to predict that, as I discuss through many pages in my declaration. 12:01:33 12:01:38 12:01:44 12:01:47 12:01:50 12:01:53

Q. You read from Column 17 that definition of "high concentration." Do you recall? 12:02:33 12:02:38 12:02:43

A. I think it was a different column than that. I didn't read it. I think I referred previously to Column 3, but we can certainly go to 17. 12:02:57 12:03:10 12:03:12 12:03:16

But I think when I -- in answering your previous question, it was Column 3 I was referring to. 12:03:18 12:03:21 12:03:25

Q. Yes. Why don't you go to Column 17. 12:03:26

A. Okay. 12:03:28

Q. About line 27 it starts. 12:03:29

A. Okay. I am there. 12:03:38

Q. It's the definition of -- it says that, "The pharmaceutical formulations of the 12:03:40 12:03:45

present invention are high concentration." 12:03:47

Do you see that? 12:03:51

A. Yes. 12:03:53

Q. And then it says, "High concentration formulations of the present invention include VEGF receptor fusion protein at a concentration of at least 41 mgs per mL, then at least 80 mgs per mL." 12:04:00 12:04:04 12:04:08 12:04:12 12:04:19

Then it continues and finishes "or at least 275 mgs per mL." 12:04:24 12:04:28

Do you see that? 12:04:31

A. Yes. I think in line 28 you left out "the pharmaceutical," but I see it's written there. So we can refer to it. But yes, it's high concentration pharmaceutical formulations. But yes, I see that. 12:04:32 12:04:33 12:04:37 12:04:40 12:04:43

Q. So is it -- in your analysis, are you assuming or using that definition that high concentration formulations are fusion receptor -- VEGF receptor formulations of at least 41 mgs per mL? 12:04:47 12:04:49 12:04:51 12:04:56 12:05:03

MS. KAYALI: Objection. Vague. 12:05:06

A. I mean, there's an alternative a couple of lines down at 35, but when you say am I using it in my declaration, where are you referring to? 12:05:08 12:05:15 12:05:17 12:05:22

BY MR. KANE: 12:05:23

Q. Well, I just -- you've been referring to "high concentration," and I just want to understand, when you say "high concentration," what do you mean? Are you using this or some other terminology? 12:05:23 12:05:26 12:05:28 12:05:31 12:05:33

A. I think I was referring to the high concentration in Column 2, and I think it's -- because you asked about the invention early on and what the need was, and I was just referring to that high concentration there, which isn't, I mean, we can enumerate. I discuss the concentrations in the claims, of course, a lot. 12:05:39 12:05:42 12:05:48 12:05:52 12:05:55 12:06:00 12:06:05 12:06:08

Q. Let's do that. Look at Claim 1 for me, please. 12:06:10 12:06:12

A. Okay. I am there. 12:06:32

Q. With respect to the aqueous 12:06:40

pharmaceutical formulation in the claim, it requires that the concentration that -- that, "aflibercept must have a concentration of at least 100 mgs per ml." 12:06:43 12:06:47 12:06:52 12:06:55

Do you see that? 12:06:58

A. Yes. Of the VEGF receptor, yeah, of the specific one referred to, yes. 12:07:04 12:07:07

Q. And the formulation must have a viscosity of about 5 to 15 centipoise at 20 degrees C? 12:07:10 12:07:12 12:07:15

MS. KAYALI: Counsel, could I just ask you to speak up a little bit. It's difficult to hear things. 12:07:17 12:07:18 12:07:19

MR. KANE: Sure. 12:07:21

BY MR. KANE: 12:07:21

Q. And the formulation must have a viscosity of about 5 to 15 centipoise at 20 degrees C? 12:07:21 12:07:22 12:07:27

A. Yes. 12:07:33

Q. Claim 1 does not include any requirement of a buffer? 12:07:36 12:07:38

MS. KAYALI: Objection. Vague. 12:07:43

A. I agree there's no word "buffer" there in Claim 1. And I discuss exactly this point extensively in my report starting at page 217, about buffer, Claim 1; really all the claims. 12:08:20 12:08:25 12:08:32 12:08:38

So it's a pretty hefty analysis. I think over 50 pages on that particular point that we can go to. 12:08:44 12:08:48 12:08:52

BY MR. KANE: 12:08:59

Q. Well, we would agree that the claim does not recite a buffer. 12:08:59 12:09:00

MS. KAYALI: Objection. Form. 12:09:12

A. As I said, I think we agree that the claim does not include the term "buffer." And I discuss, given the specification, how the skilled person would understand "buffer" with respect to Claim 1, and, of course, the other claims starting -- I mean, the whole report is important, but specifically starting at page 217 on that. 12:09:17 12:09:20 12:09:25 12:09:29 12:09:33 12:09:37 12:09:40 12:09:43

So I have extensive analysis on that point. I can go through it, but I just want to give a concise answer at this point. 12:09:46 12:09:48 12:09:53

BY MR. KANE: 12:10:00

Q. The claim -- Claim 1 does not include any specific excipients, correct? 12:10:00 12:10:02

A. Again, a similar point, now I think we'd have to go back to page -- what was it now? I thought I had it right here. 12:10:20 12:10:24 12:10:30

Sorry, 161. And I discuss this throughout, but I agree, there's not a specific excipient in the claim, but I analyze this now over 100 pages. 12:10:33 12:10:36 12:10:38 12:10:44

Q. Claim 1 does not require a particular pH? 12:10:48 12:10:50

A. Again, a similar point. I agree that a particular pH is not in Claim 1, and again, I analyze this throughout the report, for example, starting at page 161, for over 100 pages. 12:11:01 12:11:04 12:11:11 12:11:17 12:11:21

Q. Claim 1 does not include any limitations requiring stability, isn't that right? 12:11:25 12:11:30 12:11:37

A. And I'm just answering your questions as you're asking them. So these high-level 12:11:45 12:11:47

questions, so I agree there's not a specific stability limitation in the claim. And again, I've analyzed exactly these points and go to how the skilled person would understand them. 12:11:51 12:11:55 12:12:00 12:12:05

But I've analyzed these, for example, in my "Written Description" section, page 161. You may have something more specific, but just at a high level, that's how I would answer those questions. 12:12:07 12:12:10 12:12:14 12:12:17 12:12:19

Q. So with respect to stability, what is your analysis for Claim 1? 12:12:49 12:12:55

MS. KAYALI: Objection. Vague. 12:13:12

A. (Witness reviews document.) 12:13:13

With respect to stability, I mean, I can summarize my analysis. 12:14:20 12:14:22

The inventors discuss stability, for example, in Column 2, at the very beginning, as we discussed, and then also in many of the examples in the patent. I discussed stability extensively in my report. We talked about aggregation and how at higher concentrations, there tends to be, just in general, more 12:14:25 12:14:28 12:14:34 12:14:40 12:14:47 12:14:50 12:14:53

susceptibility to aggregation. 12:14:57

The inventors clearly took that into 12:15:00

account because they did analyses. We can go 12:15:01

to those examples, if you want. And I agree, 12:15:07

stability is not an explicit limitation. 12:15:11

There's no explicit stability limitation. 12:15:18

Stability isn't an issue. 12:15:23

Clearly, the -- this is a method 12:15:27

claim, so clearly it's about a -- and I'm 12:15:28

quoting from 1 -- it's Claim 1. It's about 12:15:35

administering intravitreal into an eye of the 12:15:38

subject. So it has to be suitable. One has 12:15:43

to be able to administer it intravitreally. 12:15:48

So at the time of administration, you know, it 12:15:52

can't have particulates and these sort of 12:15:55

things that would not be desired. I think 12:15:58

that's kind of evident, but I'm sure medical 12:16:03

doctors would agree, in addition to 12:16:06

formulation scientists, but there doesn't have 12:16:09

to have stability per se per the claim. 12:16:12

BY MR. KANE: 12:16:28

Q. So it has to have stability at the 12:16:28

time of injection, up until the time of injection; is that what you're saying? 12:16:34 12:16:38

MS. KAYALI: Objection. Foundation. 12:16:43 12:16:44

A. I don't think that's what I said. 12:16:48

What I said was the inventors clearly took into account stability, including at the very beginning, for example, Column 2 and maybe before that, this is what my eyes caught as you were asking that previous question, there's stability information in the examples and data, particularly with respect to aggregation. 12:16:52 12:16:57 12:17:00 12:17:02 12:17:08 12:17:10 12:17:14 12:17:16

I discuss stability aggregation in particular throughout my report, but there's no stability limitation. Stability is not in Claim 1, as we have been discussing. 12:17:19 12:17:21 12:17:26 12:17:31

Having said that, maybe this is what you were getting to, but I would want to stick to the answer the way I said it. I mean, clearly it has to be able to be administered intravitreally, and there are various -- if 12:17:36 12:17:38 12:17:40 12:17:44 12:17:48

it's degraded in various ways, it wouldn't be suitable for that or couldn't be administered intravitreally. So particulates being one example. 12:17:56 12:17:59 12:18:02 12:18:05

So it -- at the time of injection, it has to not have undesirable characteristics, particulates, various others for injection. 12:18:05 12:18:07 12:18:15

Q. Okay. And I think you're understanding what I'm trying to just drill down with you on is stability is often associated with shelf life for a commercial product. 12:18:20 12:18:21 12:18:25 12:18:34 12:18:40

Do you understand that? 12:18:41

MS. KAYALI: Objection. Foundation. Vague. 12:18:44 12:18:46

A. I mean, if what you're saying is stability is often associated with a dynamic process based on time, shelf life is a time, certain amount of time, generally Delta T. if you're making that connection, then I would agree with that time. 12:18:50 12:18:52 12:18:56 12:19:02 12:19:04 12:19:07

BY MR. KANE: 12:19:09

Q. And that's the connection I was making. So in my -- if a product -- an approved product had these specifications -- 12:19:09 12:19:11 12:19:21

A. I'm sorry? 12:19:28

Q. If an approved product had release specifications with a -- how do I want to say this. 12:19:29 12:19:31 12:19:44

Let's assume that the -- let's assume that an approved product has a shelf life with specifications for these degradation products, potentially aggregates of 12 months; does that make sense? 12:19:46 12:20:03 12:20:07 12:20:10 12:20:18

A. I don't think the way you said it makes sense, but I think I understand what you're trying to say. 12:20:23 12:20:24 12:20:28

Q. And in my hypothetical, assuming during that 12-month shelf life of that approved product it stays within its specifications, so it is suitable for intravitreal injection. Okay? 12:20:35 12:20:37 12:20:40 12:20:43 12:20:45

A. I mean, I hear you. 12:20:54

Q. All right. So under the way I think 12:20:56

you're formulating this then, it would be suitable for intravitreal -- it would be stable in the sense that it would be suitable for intravitreal injection during that 12-month -- in that 12-month window, correct? 12:21:00 12:21:02 12:21:04 12:21:07 12:21:10 12:21:14

MS. KAYALI: Objection. Vague. Foundation. 12:21:20 12:21:23

A. If I understand your hypothetical, you're just defining a time period at which it's suitable for intravitreal administration. 12:21:27 12:21:31 12:21:36

BY MR. KANE: 12:21:39

Q. Yes. 12:21:39

A. Okay. 12:21:41

Q. Okay. So let's assume at 12 months and two weeks, it's now got aggregates that exceed the specification. It's no longer suitable for intravitreal injection, correct? 12:21:42 12:21:44 12:21:49 12:21:54 12:21:57

MS. KAYALI: Objection. Foundation. Vague. 12:22:02 12:22:02

A. I don't think those kind of things are 12:22:09

in the claim. There's no shelf life or -- 12:22:12
BY MR. KANE: 12:22:18
Q. Well, I know. I'm trying to -- I'm 12:22:18
trying to understand your -- this suitability 12:22:19
for injection that you have introduced, or 12:22:21
stability for injection, and I'm just trying 12:22:25
to do it in the context of this. 12:22:27
If there's a better way to understand 12:22:30
it, please help me. 12:22:31
I guess think about it this way: If 12:22:34
the aggregates aren't present before 12 months 12:22:35
and two weeks, you would say it's stable in 12:22:38
the sense that it could be injected? 12:22:42
MS. KAYALI: Objection. 12:22:45
Foundation. Mischaracterizes testimony. 12:22:48
A. I don't think that's what I've been 12:22:54
saying. I can try to reproduce it, but I 12:22:55
would stick to what I've been saying. 12:22:58
BY MR. KANE: 12:23:00
Q. So -- 12:23:00
MS. KAYALI: Please let the 12:23:01
witness finish. 12:23:02

THE WITNESS: Thank you. 12:23:04

A. And in addition, I think you 12:23:04

mischaracterized something with respect to 12:23:07

stability. I think I -- as I emphasized, 12:23:11

there's not a stability limitation in this 12:23:15

claim. It has to be able to be 12:23:18

administered -- administered intravitreally 12:23:20

into the eye of a subject, as is stated. 12:23:24

BY MR. KANE: 12:23:30

Q. Well, why did you bring that up if you 12:23:30

said there's no stability? If that's not 12:23:31

related to stability, why are you saying 12:23:34

that? 12:23:35

MS. KAYALI: Objection. Vague. 12:23:38

A. I mean, you're -- I'm saying it 12:23:41

because you're asking me about stability, and 12:23:45

I'm answering your questions about 12:23:47

stability. 12:23:50

BY MR. KANE: 12:23:51

Q. Well, right. And so you -- you are 12:23:51

the -- you introduced the idea that it has to 12:23:53

be suitable for injection when I asked you a 12:23:55

question about stability, correct? 12:24:00

A. I think that's -- 12:24:04

MS. KAYALI: Objection. 12:24:07

Misstates prior testimony, but you can answer. 12:24:07

A. Oh, I -- okay. I understood you were 12:24:13

asking me about what you were asking, not my 12:24:17

testimony, but I think you were asking 12:24:19

something like that, and I was trying to 12:24:22

clarify the meaning with respect to stability. 12:24:25

BY MR. KANE: 12:24:36

Q. Right. I asked -- again, let me go 12:24:36

all the way back, try to get on the same page. 12:24:37

I asked you whether there was a 12:24:40

specific stability requirement in the claim. 12:24:41

So I'll ask you again, is there a 12:24:47

specific stability requirement in the claim? 12:24:48

A. Just to be clear, I'm not sure if 12:24:57

that's exactly what you asked in the past, but 12:24:58

fine, that's your question now, so I'll answer 12:25:00

the question now. 12:25:02

No, there's no stability limitation in 12:25:04

the claim. It doesn't have a stability 12:25:07

limitation per se, but I explained how the skilled person would understand the claim in terms of administering intravitreally into an eye of the subject. 12:25:12 12:25:15 12:25:18 12:25:22

Q. And you're saying that administering intravitreally into the eye of a subject relates to stability? 12:25:27 12:25:28 12:25:30

MS. KAYALI: Objection. 12:25:32

BY MR. KANE: 12:25:32

Q. Correct? 12:25:32

MS. KAYALI: Foundation. Mischaracterizes testimony. 12:25:33 12:25:35

A. No. I'm -- I'm saying that -- I mean, you could say everything is -- all these things are related in terms of formulation. 12:25:41 12:25:46 12:25:48

What I'm saying is there's not a stability limitation here per se. But we talked about the term "suitable." I think that's fine and I've raised it, so fine, but it's not in the claim, but it's -- I mean, I think it's evident that it has to be administered intra- -- it has to be able to be 12:25:52 12:25:53 12:25:57 12:25:59 12:26:03 12:26:06 12:26:09

administered intravitreally into the eye of the subject. 12:26:12 12:26:16

There's no stability limitation in terms of time here or anything, but it has to be suitable or the doctor has to be able to administer it at the time. 12:26:17 12:26:19 12:26:26 12:26:28

BY MR. KANE: 12:26:32

Q. Okay. And so at the time, you're pointing to the time of administration, correct? 12:26:32 12:26:40 12:26:51

A. That's what I said, that's how I'm reading this. It's about administering -- it's a method, and it has to do with -- I mean, there's more, but administering intravitreally into an eye of the subject. 12:26:51 12:26:53 12:26:54 12:26:57 12:26:58

Q. Okay. And what I'm trying to understand is, if a formulation is made today and it's suitable for administration to a patient today, is that a stable formulation? 12:27:04 12:27:05 12:27:21 12:27:24

MS. KAYALI: Objection. Incomplete hypothetical. Foundation. 12:27:40 12:27:42

A. I think you're somehow mixing 12:27:47

concepts. Today is a moment in time. Well, I guess today is 24 hours in time, whatever, but I think you're implying that that's a moment. 12:27:51 12:27:59 12:28:01

Stability has to do with over a period of time, so they're kind of different concepts. 12:28:06 12:28:09 12:28:11

BY MR. KANE: 12:28:12

Q. Okay. That's what -- right. And so the next step in my hypothetical would be, that formulation that's suitable for injection today is not suitable for injection a week from today. Is that formulation stable? 12:28:12 12:28:15 12:28:20 12:28:24 12:28:28

MS. KAYALI: Objection. Incomplete hypothetical. Foundation. 12:28:36 12:28:37

A. I mean, it depends on -- I mean, again, I think stability isn't part of the claim, and it depends on the reason. I mean, I'd like to know what happened and whatnot, but I'm not sure. 12:28:42 12:28:48 12:28:51 12:28:59 12:29:07

If you can't inject it intravitreally into the eye of a subject, then it's not part of the claim. So if it has particulates or 12:29:08 12:29:10 12:29:13

whatever -- 12:29:16
BY MR. KANE: 12:29:18
Q. Right. 12:29:18
MS. KAYALI: Sorry. Are you 12:29:18
finished, Dr. Trout? 12:29:19
THE WITNESS: No. 12:29:22
A. Then I agree it's not part of the 12:29:23
claim. If you make it and you can inject it, 12:29:24
whatever, and it meets all the limitations, 12:29:30
then it falls under the claim. 12:29:32
BY MR. KANE: 12:30:17
Q. Okay. The claim has a concentration 12:30:17
limitation of at least 100 milligrams per 12:30:21
milliliter, correct? 12:30:28
A. Yes, of the VEGF receptor fusion 12:30:29
protein, and I discuss in my report how the 12:30:33
skilled person would understand that. 12:30:36
Q. The claim does not have an upper 12:30:41
limit, correct? 12:30:42
MS. KAYALI: Objection. 12:30:47
Foundation. Calls for a legal conclusion. 12:30:50
BY MR. KANE: 12:30:53

Q. And let me ask this question, the claim does not recite an upper limit, does it? 12:30:53 12:30:54 12:30:56

MS. KAYALI: Objection. Foundation. Calls for a legal conclusion. 12:31:04 12:31:06

A. (Witness reviews document.) 12:31:46

Okay, found it, found what I was looking for. 12:32:02 12:32:03

So I agree, there's the one number, and you read it correctly, at least 100 milligrams per milliliter, again, of the VEGF receptor fusion protein; but again, I understand a skilled person would read that, and as I have elaborated starting on page 187, 187. 12:32:10 12:32:13 12:32:17 12:32:19 12:32:26 12:32:28 12:32:37

Q. Okay, I'm there. 12:32:43

A. Okay, thanks. 12:32:44

Starting at Paragraph 262, but really the header, little letter b, Claim 1, has an implicit upper concentration limit of about 160 mgs per mL, and I have extensive analysis of why I've come to that conclusion in 12:32:46 12:32:49 12:32:55 12:32:58 12:33:03

subsequent pages. 12:33:07

So that's how the skilled person would understand the upper limit of Claim 1. 12:33:08 12:33:10

Q. And you're basing the upper limit on the examples in the specification? 12:33:44 12:33:47

MS. KAYALI: Objection. Foundation. 12:33:52 12:33:54

BY MR. KANE: 12:33:55

Q. I'm reading -- I'm looking at Paragraph 262 where you say, "There are no examples of VEGF fusion protein concentrations above 155 mgs per milliliter that achieve the required viscosities." 12:33:55 12:33:56 12:33:59 12:34:02 12:34:07

A. Well, I'm -- I mean, that's a quote from Dr. Falconer, but I include that quote in Paragraph 262, correct. 12:34:24 12:34:25 12:34:31

Q. Right. 12:34:32

A. I'm addressing -- I mean, literally the first words of the paragraph are, "Dr. Falconer opines." I'm addressing his opinions and quoting part of those opinions. 12:34:32 12:34:35 12:34:37 12:34:41

Q. Okay. But then on the next -- you 12:34:44

continue to the next page. At the top you say, "The POSA" -- this is you speaking, correct? 12:34:51 12:34:54 12:34:56

A. Very top of 188? 12:35:00

Q. Yes. 12:35:03

A. Yes. 12:35:03

Q. "...also would recognize that the numerous low viscosity formulations comprising up to 155 mgs per mL of aflibercept," those are the examples in the specification, correct? 12:35:03 12:35:06 12:35:08 12:35:14 12:35:18

MS. KAYALI: Objection. Vague. 12:35:23

A. And I'm referring to the patent and the specification, yes. 12:35:25 12:35:30

BY MR. KANE: 12:35:32

Q. Okay. "As demonstrating the inventor's possession of low viscosity formulations with concentrations between 100 and around 160 mgs per mL." 12:35:32 12:35:33 12:35:36 12:35:38

Do you see that? 12:35:41

A. Yes. 12:35:46

Q. Okay. So you -- you relied upon the 12:35:47

examples in the specification to arrive at your 160 mg per mL limit, correct? 12:35:49 12:35:52

MS. KAYALI: Objection. Foundation. 12:35:59 12:36:05

A. I mean, if by "relied" you mean I took them into account and I used other things, as I discuss, I mean, this is a many-page discussion, but certainly examples are part of it. 12:36:05 12:36:09 12:36:13 12:36:17 12:36:20

BY MR. KANE: 12:36:22

Q. Okay. And the examples in the specification had two buffers, I believe? 12:36:22 12:36:23

MS. KAYALI: Objection. Vague. Foundation. 12:36:34 12:36:37

A. Well, I -- you should point to what you have in mind. 12:36:37 12:36:40

BY MR. KANE: 12:36:42

Q. Sure. What I meant is there were two -- there were formulations with histidine buffers and phosphate buffers in the specification, correct, where they measured viscosity? 12:36:42 12:36:45 12:36:48 12:36:50 12:36:55

1	For instance, look at Figure 9, or	12:37:03
2	look at Figure 10.	12:37:05
3	A. (Witness reviews document.)	12:37:32
4	I mean, we can go through all of this.	12:38:21
5	The figure -- I'm just looking now at the	12:38:26
6	Table 9-3. I'd have to go back.	12:38:29
7	I've done this before, but I'd have to	12:38:35
8	go back and map the different bars to what's	12:38:36
9	in the tables. But I mean, just -- there's --	12:38:43
10	certainly in Figures 9 and 10 there's mention	12:38:48
11	of histidine. But in Table 9.3 there's sodium	12:38:52
12	citrate, for example.	12:38:58
13	I think I discuss in my report and go	12:39:03
14	to that arginine can also have buffering	12:39:04
15	capacity, but that's, you know, a different --	12:39:07
16	so -- and then, of course, there's the --	12:39:11
17	there's the protein itself which I discuss	12:39:14
18	extensively in my report, if that's what	12:39:18
19	you -- I mean, we can go to other tables if	12:39:21
20	you want.	12:39:24
21	I have a section on this towards the	12:39:24
22	end of my report we can also go to.	12:39:26

Q. Does buffer have -- does the buffer selection have an impact on the viscosity of formulation? 12:39:29 12:40:57 12:41:00

MS. KAYALI: Objection. Vague. 12:41:02

A. I mean, there's a lot of data here reported for different formulations. I could go and look if there's specific swapping out of buffers. 12:41:42 12:41:45 12:41:52 12:41:54

Again, what one puts in a formulation can certainly affect viscosity. When there's no information, there are these general strategies but no adequate predictive approaches. 12:41:59 12:42:05 12:42:11 12:42:15 12:42:18

As one develops understanding, as I've elaborated here, on a specific system, one gets an understanding of the robustness of various formulations and whatnot. I, again, discuss this. It's a really short summary of 100-plus pages in my written description section. 12:42:23 12:42:25 12:42:27 12:42:31 12:42:34 12:42:39 12:42:42

BY MR. KANE: 12:42:42

Q. If a formulator was able to formulate 12:42:42

aflibercept at 180 milligrams per milliliter and otherwise satisfy all the limitations of Claim 1, would it be covered by Claim 1? 12:42:51 12:43:01 12:43:04

MS. KAYALI: Objection. Incomplete hypothetical. 12:43:09 12:43:12

A. (Witness reviews document.) 12:44:00

Sorry, I'm just trying to find where I was in the report to answer your question. 12:44:01 12:44:03

Here we go. Okay, I found it. 12:44:15

I'd have to do that analysis. I was -- I'm addressing how the skilled person would read this claim in response to Dr. Falconer's opinions. I don't think he brought up that question in particular -- 12:44:25 12:44:30 12:44:36 12:44:39 12:44:42

Q. Well -- 12:44:46

A. -- and this isn't an infringement analysis, so I -- I'd have to understand the specifics. 12:44:47 12:44:49 12:44:53

Q. Well, I'm looking at your opinion, page 187, 262. 12:44:54 12:44:56

A. Okay. 12:45:00

Q. You're like me, having to go back and 12:45:03

forth with the glasses. 12:45:04

A. Sorry? 12:45:05

Q. You're like me, going back and forth 12:45:06

with the glasses. 12:45:08

A. Yeah, thank you. I have progressive 12:45:09

lenses, but it's easier to read if you're 12:45:10

doing a lot of reading. 12:45:13

Q. So the last sentence, you say, "I 12:45:15

disagree that Claim 1 lacks adequate written 12:45:18

description, as the POSA would recognize that 12:45:21

Claim 1 is limited to a workable upper 12:45:25

concentration limit of around 160 milligrams 12:45:27

per milliliter." 12:45:33

Correct? 12:45:37

A. Yes. 12:45:38

Q. I read that right? 12:45:39

A. You did; you did read it correctly. 12:45:40

Q. So that is your opinion. So when you 12:45:43

say Claim 1 is limited, does that mean it does 12:45:45

not cover formulations above 160 mgs per 12:45:48

milliliter? 12:45:59

MS. KAYALI: Objection. Calls 12:45:59

for a legal conclusion. Outside the scope. 12:46:02

A. What I'm saying is that the skilled person would understand, as I say, the workable upper concentration limit is around 160 milligrams per milliliter. 12:46:05 12:46:07 12:46:11 12:46:15

I understand 180 is greater than that. If there were a formulation as such, I would want to do an analysis, a detailed analysis to understand; but I agree 180 would be above 160. But Dr. Falconer didn't raise that point and I have to analyze the specifics to determine that. 12:46:20 12:46:23 12:46:30 12:46:37 12:46:39 12:46:44 12:46:48

BY MR. KANE: 12:46:53

Q. Well, I think Dr. Falconer is raising that issue, right? His opinion is that the claim covers all concentrations above 180 mgs per mL -- or, excuse me, 100 mgs per mL. 12:46:53 12:46:56 12:46:58 12:47:03

Your opinion is that there's some workable upper limit at 160. 12:47:09 12:47:11

So the question is, would -- under your analysis, would a formulation greater than 160 be covered by the claim? 12:47:16 12:47:22 12:47:26

MS. KAYALI: Objection. Misstates the record. Lacks foundation. Outside the scope. 12:47:30 12:47:31 12:47:37

A. And just to be clear, I specifically state "workable upper concentration limit of around 160." 12:47:39 12:47:42 12:47:44

BY MR. KANE: 12:47:47

Q. I understand. 12:47:48

A. You dropped the "around," so I just want to -- 12:47:48 12:47:50

Q. I didn't -- I didn't mean to. 12:47:50

A. Okay, okay, fine. 12:47:51

Q. I think we can agree that 180 is not around 160 mgs per mL in this context? 12:47:51 12:47:54

MS. KAYALI: Objection. Foundation. 12:47:58 12:48:02

A. I agree -- I agree that 180 is greater than 160, clearly. 12:48:09 12:48:13

Now, for a given application, I'm sure you've done this much more than I, but I've done lots of infringement analyses, and they're usually pretty extensive. So I 12:48:15 12:48:18 12:48:21 12:48:25

don't -- I have not been asked to do such analysis at 180, and I wouldn't want to do that on the fly. I'd have to look at the specifics, so -- but I -- I would stick -- I agree with what I wrote here, sitting here, and I think this is the correct way of understanding the claim. 12:48:26 12:48:28 12:48:33 12:48:35 12:48:38 12:48:41 12:48:42

BY MR. KANE: 12:48:45

Q. So what is a workable -- what does "limited to a workable upper concentration" mean then? 12:48:45 12:48:47 12:48:50

If it's -- you're saying that concentrations greater than 100 and -- this workable upper limit may still be covered by Claim 1. You would need to do an analysis in order to determine that? 12:48:53 12:48:54 12:48:58 12:49:01 12:49:05

MS. KAYALI: Objection. Foundation. 12:49:12 12:49:18

A. I'm -- I agree with what I wrote, with that caveat with the "around" where -- I think we're on board there. 12:49:18 12:49:21 12:49:24

I'm addressing Dr. Falconer's 12:49:27

opinions, which I think you summarized as that there's no upper limit. I just think that isn't reasonable. 12:49:32 12:49:34 12:49:36

I mean, it can't be infinite. So it has to be -- there has to be an upper limit, a reasonable upper limit. And I've done the analysis that I've done. This is just the beginning over many pages. 12:49:38 12:49:41 12:49:45 12:49:47 12:49:49

And yes, I've looked at the examples, among other things. And that's why I concluded that it's -- that the workable upper concentration limit is around 160. It's addressing Dr. Falconer's point that there's no upper limit. 12:49:52 12:49:54 12:49:57 12:50:04 12:50:09 12:50:14

BY MR. KANE: 12:50:15

Q. Well, there's no upper limit in the claim, we can agree with that? 12:50:15 12:50:16

So there's no number greater than 100 mgs per mL in the claim? There's only one number in the claim for concentration, correct? 12:50:18 12:50:20 12:50:23 12:50:33

A. Yes, there's one number for 12:50:33

concentration. But clearly, the skilled person would understand that there's an upper limit or workable upper limit, as I have in the top of page 188. 12:50:34 12:50:36 12:50:39 12:50:43

Q. And you arrived at that upper limit based on the data in the patent? 12:50:47 12:50:49

MS. KAYALI: Objection. Misstates prior testimony. 12:50:56 12:51:00

You can answer. 12:51:06

A. I certainly took into account the data in the patent. But I concluded, based on all the things that I discuss here, I have a lot of references, it's a multipage analysis. 12:51:06 12:51:10 12:51:13 12:51:16

I mean, it includes the data in the patent, but there's other -- other aspects to my analysis, other things that I took into account, including general knowledge. 12:51:21 12:51:23 12:51:30 12:51:32

BY MR. KANE: 12:52:09

Q. But sitting here today, you couldn't determine whether a formulation with a concentration of 180 mgs per mL, that otherwise meets the limitations of Claim 1, is 12:52:09 12:52:12 12:52:17 12:52:24

covered by Claim 1? 12:52:28

MS. KAYALI: Objection. Asked 12:52:32

and answered. Calls for a legal conclusion. 12:52:34

And outside the scope. 12:52:35

A. I didn't do that analysis. I can do 12:52:45

the analysis, if need be. I wasn't asked to 12:52:47

do it. It wasn't brought up. And I wouldn't 12:52:51

want to do such an analysis on the fly here in 12:52:54

this context. 12:52:58

I said numerous times, I agree 180 is 12:53:01

greater than 160. And if there's some 12:53:05

infringement analysis, I would want to do that 12:53:10

carefully. 12:53:13

BY MR. KANE: 12:53:15

Q. Would you have the same answer for a 12:53:15

formulation that had 200 mgs per mL? 12:53:17

A. I mean, broadly speaking, we're just 12:53:30

talking about hypotheticals here. So I want 12:53:33

to know the details and do that analysis, and 12:53:40

it hasn't been brought up before. 12:53:44

Q. Okay. 12:53:47

A. I agree 200 is higher than 180 is 12:53:48

higher than 160. 12:53:53

Q. But what details do you need? 12:53:54

A. As I've stated, I've done infringement analyses before. I'm sure you've done many more than I. You're a legal professional. And one looks -- I mean, it's generally an extensive analysis. And it's not something you can just do in a few minutes in this context. You need documents. You need to look at things. You need to think about it and understand whether it falls within the scope of the claim or not. 12:54:03 12:54:07 12:54:09 12:54:14 12:54:17 12:54:20 12:54:24 12:54:26 12:54:28 12:54:31

Q. If you look at Claim 1, it also has a limitation that the -- that "the formulation has a viscosity of about 5 to 15 centipoise at 20 degrees C." 12:54:33 12:54:44 12:54:46 12:54:51

Do you see that? 12:54:52

A. Yes. 12:54:56

Q. Would a formulation that otherwise meets all of the limitations of Claim 1 but has a viscosity of 30 degrees centipoise at 20 degrees C meet the claim? 12:54:57 12:54:58 12:55:00 12:55:05

A. I think I know what you're trying to ask. I think you didn't ask the question the way you wanted. You better -- try to state it the way I think you're asking. 12:55:16 12:55:17 12:55:23 12:55:26

Q. Why don't you just answer, yes, please. 12:55:27 12:55:29

A. I think you said 30 degrees at 20 degrees. I think you meant 30 centipoise -- 12:55:30 12:55:33

Q. Yes, that's what I meant. 12:55:38

A. -- but maybe just so we have a clean question, maybe repeat it. 12:55:40 12:55:43

Q. You're right. I did say -- okay. 12:55:46

So would a formulation that meets all of the other limitations of Claim 1 but has a viscosity of 30 centipoise at 20 degrees C be covered by Claim 1? 12:55:47 12:55:55 12:55:59 12:56:04

MS. KAYALI: Objection. Calls for a legal conclusion. Outside the scope. 12:56:09 12:56:12

A. Again, I understand that 30 is higher than 15. It's double in this case. I wouldn't want to do such an analysis on the fly. I agree 30 is greater than 15. 12:56:23 12:56:26 12:56:31 12:56:33

I mean, there are other -- I understand there are a variety of considerations that go into such an analysis, an infringement or an infringement-like analysis. I haven't been asked to do that. 12:56:39 12:56:41 12:56:43 12:56:47 12:56:51

If there's a particular product, I would want to do that and determine whether it falls within the scope of the claim or not. 12:56:53 12:56:55 12:56:58

BY MR. KANE: 12:57:01

Q. Would you agree that it doesn't, literally, fall within the scope of the claim? 12:57:01 12:57:04

MS. KAYALI: Objection. Calls for a legal conclusion. 12:57:14 12:57:17

A. I don't know. I would have to look into the details. I agree that 30 is literally greater than 15. But as you know, people say things and then as hypotheticals or statements of what they think or hope is reality and then one looks into it, and the reality is different. 12:57:17 12:57:19 12:57:22 12:57:27 12:57:33 12:57:36 12:57:39

So I would want to do the analysis, if I were asked to do that. 12:57:41 12:57:45

BY MR. KANE: 12:58:06

Q. Let's turn to Claim 31. 12:58:06

A. Okay. I am there. 12:58:17

Q. And with respect to the formulation, 12:58:25

the aqueous pharmaceutical formulation, 12:58:31

there's a requirement that the concentration 12:58:33

be about 114.3 mgs per mL -- 12:58:36

12:58:42

(Stenographer clarification.) 12:58:42

12:58:42

BY MR. KANE: 12:58:42

Q. -- 114.3 mgs per mL of aflibercept, 12:58:42

correct? 12:58:52

A. Yes, that's, I think, a paraphrasing 12:58:52

of what's stated here. 12:58:55

Q. And the "formulation must also have a 12:58:57

viscosity of about 15 to 15 [sic] centipoise 12:58:59

at 20 degrees C," correct? 12:59:04

A. No, I don't think you read it 12:59:10

correctly. 12:59:12

Q. Well, all right. 12:59:16

A. I think you just sort of made a verbal 12:59:17

typo. 12:59:19

Q. Well, the claim says that the "aqueous pharmaceutical formulation," it says "having," but it's not great English, "has a viscosity of about 5 to 15 centipoise at 20 degrees C"? 12:59:21 12:59:24 12:59:31 12:59:35 12:59:38

A. Yes. But I mean, that -- it says that, yes. I think you had said "15 to 15." That's why I'm -- thank you for correcting that. 12:59:43 12:59:47 12:59:51 12:59:53

Q. The claim does not include any limitations requiring a buffer? 12:59:55 13:00:00

MS. KAYALI: Objection. Calls for a legal conclusion. Vague. 13:00:08 13:00:17

A. (Witness reviews document.) 13:00:34

Again, I agree the word "buffer" is not in this Claim 31, and I certainly discuss this extensively as we -- as I alluded to -- well, as I stated before, for example, starting on page 217 when I talk about buffer and description, and I have an extensive analysis, close to 70 pages on this. Well, 13:00:43 13:00:47 13:00:54 13:01:01 13:01:03 13:01:10 13:01:13

sorry, 50-something pages on this, which we can refer to, if you want. 13:01:19 13:01:23

BY MR. KANE: 13:01:25

Q. Well, for instance, at 221 of your report, paragraph -- page 221. 13:01:25 13:01:27

A. Oh, okay. I'm there. 13:01:36

Q. You have a section that says, "The Specification Expressly Teaches That the 'Buffer' is Optional," right? 13:01:38 13:01:39 13:01:41

A. I mean, I have "a buffer" instead of "the buffer," but yes, that's correct. 13:01:45 13:01:50

Q. So your analysis of the specification is that it teaches that a buffer -- that a buffer is optional, right? 13:01:57 13:01:58 13:02:01

A. Yeah, it teaches that, as I discuss here. 13:02:15 13:02:17

Q. And so in Claim 31, consistent with that, a buffer is optional, correct? 13:02:18 13:02:21

MS. KAYALI: Objection. Vague. 13:02:32 13:02:33

A. I mean, as long as it's understood, as I discuss here, what you're saying is, as I 13:02:36 13:02:40

discuss here and starting on page 221, and again, buffer -- I wasn't going to make this explicit, but now I think we should. The "buffer" I have here is in quotes, and I think part of my analysis is how a skilled person would think about the protein itself. 13:02:43 13:02:48 13:02:52 13:02:54 13:02:57 13:03:01

So here I'm talking about in addition to that. That's why there's the quotes, but that's -- 13:03:05 13:03:10 13:03:14

BY MR. KANE: 13:03:15

Q. Okay. I understand. 13:03:15

A. Okay. 13:03:16

Q. When I'm using the term "buffer" here, I'm not talking about the self-buffering of the protein. I'm talking about a buffer excipient. 13:03:17 13:03:19 13:03:21 13:03:25

Do you understand that? 13:03:27

A. Okay. Yes, good. That's helpful. 13:03:30

Q. And so in Claim 31, which is a comprising claim, meaning it's not limited to what's listed in Claim 31, and consistent with your analysis of the specification, a buffer 13:03:33 13:03:38 13:03:42 13:03:49

is -- a buffer excipient is optional? 13:03:52

A. Right, just as I say, "The specification expressly teaches that a 'buffer' in quotes, is optional." And I explain all the reasons for that. 13:04:08 13:04:10 13:04:12 13:04:16

Q. And I'm just trying to tie that to Claim 31. 13:04:19 13:04:21

A. Yes. It is -- it is tied. 13:04:28

Q. So, claim -- in Claim 31, a buffer excipient is optional? 13:04:36 13:04:39

A. (Witness reviews document.) 13:05:06

I mean, I -- I think that's fair. We could -- my header covers all the claims, but I just -- I want to make clear that there's a whole section of reasoning that gets to that point. So I would also defer to all the opinions here over many pages. 13:05:14 13:05:20 13:05:24 13:05:29 13:05:34 13:05:39

Q. And Claim 31 does not recite any other specific excipients, does it? 13:05:47 13:05:51

A. I mean, if you mean by "any other," I agree that excipients; they're not specific excipients recited or written here in 13:06:13 13:06:16 13:06:20

Claim 31. I agree with that. 13:06:25

And I, again, in my written -- well, 13:06:28

throughout, but in particular the "Written 13:06:30

Description" section, I discuss how the 13:06:32

skilled person would understand the claim in 13:06:35

that light. 13:06:39

Q. And again, in the same -- just to make 13:06:50

the record clean, your opinion then is that 13:06:53

any or no excipients are required by 13:07:10

Claim 31? 13:07:16

MS. KAYALI: Objection. 13:07:17

Misstates the record. 13:07:20

BY MR. KANE: 13:07:27

Q. Well, let me say it this way: 13:07:27

Claim -- all excipients, including buffer 13:07:31

excipients, are optional in Claim 31? 13:07:37

MS. KAYALI: Objection. 13:07:49

A. Just to be clear, we certainly -- we 13:08:12

certainly have that header with the quote, 13:08:16

"buffer," end quote. But I have -- I don't 13:08:19

think I say that here. 13:08:24

I do an extensive analysis of the 13:08:27

description with respect to the various excipients and buffers, excipient buffers as you call them, in my written description analysis, which is over 100 pages. I wouldn't summarize it just like that. 13:08:30 13:08:32 13:08:37 13:08:42 13:08:47

BY MR. KANE: 13:08:50

Q. So in your analysis, did you identify any excipients that are required in the formulation of Claim 31? 13:08:50 13:08:53 13:08:58

A. No. And as I've stated, and I stick to that, it's correct. I think, frankly, we all agree, there are not specific excipients that are required, as you ask, in Claim 31. 13:09:16 13:09:21 13:09:24 13:09:28

And I discuss the various formulations that encompass excipients, for example, starting on page 165, and that's Claim 1, but I have a similar analysis for 31. I can find that, if you want, and talk about the extensive formulations here and why the claims, including Claim 31, are adequately described. 13:09:35 13:09:39 13:09:44 13:09:49 13:09:52 13:09:55 13:10:00 13:10:03

Q. But that's not the question I was 13:10:05

asking. 13:10:06
All I'm -- let's look back at -- look 13:10:11
at Claim 9 for me, please. 13:10:13
A. Okay. 13:10:21
Q. Do you understand that's a dependent 13:10:21
claim from Claim 1? 13:10:24
A. Yes. 13:10:35
Q. And you understand the concept of 13:10:36
independent and dependent claims, right? 13:10:38
A. I think so. You're the attorney, 13:10:41
so... 13:10:43
Q. So you would understand -- 13:10:43
A. I think I have a working 13:10:44
understanding. 13:10:45
Q. You would understand that Claim 9 13:10:46
requires the method of Claim 1, wherein the 13:10:48
formulation comprises a sugar, right? 13:10:53
A. Yes. Again, given the caveats; but in 13:11:02
broad terms, yes, that's what's written here. 13:11:07
Q. Right. And, for instance, that type 13:11:12
-- and that's a specific excipient, a sugar? 13:11:12
MS. KAYALI: Objection. Vague. 13:11:20

A. I think -- I think it's a category. 13:11:24
We should probably go -- 13:11:28
BY MR. KANE: 13:11:29
Q. I was going to say -- 13:11:29
MS. KAYALI: Dr. Trout, were you 13:11:30
finished with your answer? 13:11:31
THE WITNESS: No. 13:11:32
MS. KAYALI: Counsel, I will ask 13:11:34
that you allow the witness to answer the 13:11:35
question that you've asked. 13:11:37
MR. KANE: I withdraw the 13:11:38
question. I want to ask a different question. 13:11:39
BY MR. KANE: 13:11:41
Q. Let's look at Claim 10. "The method 13:11:41
of Claim 10 wherein -- the method of Claim 1 13:11:45
wherein the formulation comprises sucrose, 13:11:48
trehalose, sorbitol, mannitol, propanesulfonic 13:11:54
acid, or glycerol." 13:11:58
Do you see that? 13:12:03
A. Yes. 13:12:07
Q. You would agree with me that that is a 13:12:07
list of excipients? 13:12:08

A. Yes. 13:12:16

Q. And in contrast to Claim 10, Claim 1 and Claim 31 do not have a list or identify specific excipients, correct? 13:12:20 13:12:23 13:12:27

MS. KAYALI: Objection. Vague. 13:12:37

You can answer. 13:12:37

A. Yes. There aren't specific excipients in those claims. And again, the skilled person would understand them, as I discussed here in my written description section. 13:12:38 13:12:42 13:12:45 13:12:47

BY MR. KANE: 13:13:14

Q. To close it out, go to Claim 35. 13:13:14

So this is another independent claim, correct? 13:13:22 13:13:32

A. Yes. 13:13:32

Q. Claim 35, like Claim 1 and like Claim 31, does not recite any specific excipients, right? 13:13:34 13:13:41 13:13:45

A. I agree there's not -- there are not specific excipients in Claim 35, and I discuss the significance of this in the "Written Description" section of my report, in 13:14:09 13:14:12 13:14:19 13:14:21

particular in the section starting on page 203, but throughout the report. 13:14:25 13:14:27

Q. And Claim 35 does not recite any stability requirement? 13:14:55 13:15:01

A. Yes, I agree there's not a specific stability requirement, as we discussed over time. I mean, clearly, the administration -- the intravitreal administration, that being administrated, has to be suitable. You know, that word isn't here, but I think we understand what that means. It has to be able to be administered. 13:15:11 13:15:14 13:15:18 13:15:26 13:15:31 13:15:34 13:15:36 13:15:38

Q. So Claim 35 would cover a formulation that meets the recited language regardless of the excipients used in the formulation? 13:16:31 13:16:39 13:16:45

MS. KAYALI: Objection. Vague. 13:16:55

A. I mean, again, I think if one were to -- one would have to look at the specifics of a given formulation. 13:16:57 13:17:04 13:17:08

I agree that in Claim 35, there are no specific excipients required. It can't be regardless. It has to be -- it has to be 13:17:12 13:17:16 13:17:24

administered intravitreally. 13:17:27
BY MR. KANE: 13:17:31
Q. Understood. And the question was, if 13:17:31
the formulation meets all the requirements 13:17:34
recited in Claim 35, it would cover -- it 13:17:44
would be covered regardless of the excipients 13:17:51
used. 13:17:53
MS. KAYALI: Objection. Vague. 13:17:56
A. I think if there's a specific 13:18:02
instantiation, one would have to do an 13:18:08
analysis of it; but I think my opinions in 13:18:11
this declaration are that there are no 13:18:17
specific excipients required in Claim 35. 13:18:21
I would stick to the way I'm saying it 13:18:27
and not try to kind of turn it around and see. 13:18:29
That's what I would say. There's no specific 13:18:33
excipients required in Claim 35. 13:18:36
BY MR. KANE: 13:18:44
Q. And so a formulation that meets the 13:18:44
requirements of Claim 35 and uses a sodium 13:18:46
phosphate buffer would still be included in 13:18:51
Claim 35? 13:18:54

A. Certainly sodium phosphate is used in some of the examples in the specification. In general, it meets all these, and it has sodium phosphate. I would think it would be covered. 13:19:26 13:19:30 13:19:35 13:19:41

Again, I know people have specific reasons why something might or might not be covered when one does such an infringement analysis, but I agree sodium phosphate is discussed in the specification, and one would generally think it could be incorporated here. 13:19:45 13:19:50 13:19:52 13:19:54 13:20:02 13:20:07

Q. The same with the histidine buffers? 13:20:11

A. Yeah, that's the same. And then the other -- and again, I think I -- as I discussed, histidine doesn't necessarily have to fall under a category of buffer, per se. I have several pages of analysis of that. But those are specifically discussed here. And I do an analysis of the extensive representative formulations in the patent, too. 13:20:19 13:20:22 13:20:25 13:20:28 13:20:31 13:20:36 13:20:39 13:20:44

MS. KAYALI: Counsel, I don't want to interrupt you. I would just let you know that food is here. 13:21:14 13:21:14 13:21:17

MR. KANE: It's probably a good break. 13:21:19 13:21:20

THE VIDEOGRAPHER: This is the end of Media No. 3. We are going off the record. The time is 1:22 p.m. 13:21:22 13:21:22 13:21:26

13:23:28

(Recess taken from 1:22 p.m. to 2:07 p.m.) 13:23:28 13:23:28 13:23:28

14:06:35

THE VIDEOGRAPHER: This is the beginning of Media No. 4. We are going back on the record. The time is 2:07 p.m. 14:06:35 14:06:35 14:06:39

BY MR. KANE: 14:06:42

Q. Welcome back, Dr. Trout. 14:06:42

I'm handing you what's previously been marked as Alvotech 1005, and you analyzed this patent as part of your declaration, correct? 14:06:49 14:06:53 14:07:02

A. Yes. 14:07:21

Q. And we talked about this a little bit earlier, but you can see that it's issued on October 27, 2009 in the upper right-hand corner and claims priority back to a 14:07:28 14:07:30 14:07:34 14:07:38

provisional application June 16, 2006. 14:07:42

Do you see that? 14:07:47

A. Yes. 14:07:51

Q. And it's -- the assignee is Regeneron Pharmaceuticals, Inc., correct? 14:07:56

A. Yes. 14:08:04

Q. It's entitled "VEGF Antagonist Formulations Suitable for Intravitreal Administration," right? 14:08:05

A. Yes. 14:08:17

Q. And then in the abstract, it also refers to "Preferably the protein antagonist has the amino acid sequence shown in SEQ ID NO:4," right? 14:08:31

A. Yes, that's the last sentence of the abstract. 14:09:01

Q. Okay. And SEQ ID NO:4 is aflibercept? 14:09:02

A. Yeah. I mean, that's -- that's right. 14:09:03

Q. Okay. If you look at Column 1, if we -- and starting at line 1, "The invention includes liquid pharmaceutical formulations having increased stability, as well as 14:09:26 14:09:48 14:09:59 14:10:03 14:10:07

formulations that may be lyophilized and reconstituted for intravitreal administration," correct? 14:10:10 14:10:15 14:10:17

A. Yes, that's the sentence. 14:10:20

Q. Okay. If you look at Column 2, line 4, the paragraph states, "In one aspect, a stable liquid ophthalmic formulation is provided that comprises 1 to 100 mgs per mL, VEGF specific fusion protein antagonist, 0.01 to 5 percent of one or more organic cosolvents, 30 to 150 millimolar of one or more tonicity agents, 5 to 40 millimolar of a buffering agent, and optionally, 1 to 7.5 percent of a stabilizing agent, pH between about 5.8 to 7," correct? 14:10:28 14:11:29 14:11:39 14:11:43 14:11:51 14:11:58 14:12:02 14:12:07 14:12:12 14:12:17 14:12:21

A. Yes. 14:12:32

Q. Okay. Let's look at Claim 1. 14:12:45

You see that Claim 1 is directed to "An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist comprising," and then it has A, B, C, and D below it? 14:13:12 14:13:14 14:13:19 14:13:24 14:13:28

A. Yes. 14:13:30

Q. Okay. And the first one, A, says, "1 to 100 mgs per mL of a VEGF antagonist comprising the amino acid Sequence ID NO:4," correct? 14:13:37 14:13:40 14:13:44 14:13:52

A. Yes. 14:13:54

Q. Okay. So a formulation that -- so Furfine is teaching aflibercept formulations of up to 100 mgs per mL of aflibercept, correct? 14:14:04 14:14:32 14:14:35 14:14:41

A. I mean, I think that's correct. I mean, there are other limitations, but if we're talking about Claim 1, but yes, it's 1 to 100 mgs per mL, correct. 14:14:53 14:14:56 14:15:01 14:15:04

Q. Okay. And that would -- and that formulation is suitable for intravitreal injection, correct? 14:15:08 14:15:10 14:15:14

MS. KAYALI: Objection. Vague. 14:15:17

A. I mean, given the terminology, it's an ophthalmic formulation, so it can be injected into the eye, I would say, intravitreally. 14:15:20 14:15:27 14:15:33

BY MR. KANE: 14:15:50

Q. Okay. Like the claims that we looked at in the '036 patent, it doesn't have a specific stability limitation, does it? 14:15:50 14:15:53 14:15:58

A. Correct. I think that's fair. 14:16:10

Q. So would your analysis be the same for this -- these ophthalmic formulations here, that as long as they -- that they have to be suitable for administration at the time of an injection? 14:16:19 14:16:22 14:16:26 14:16:29 14:16:35

MS. KAYALI: Objection. Vague. 14:16:41

A. Again, as I understand your question, and we didn't define "suitable" per se, but I agree that one has to be able to inject it. You can't have particulates and these sort of things that we discussed before. 14:16:45 14:16:53 14:16:58 14:17:06 14:17:09

BY MR. KANE: 14:17:34

Q. Okay. You saw earlier that this patent describes both stable liquid formulations and lyophilizable formulations. 14:17:34 14:17:41 14:17:44

Do you see that? 14:17:50

A. I mean, as long as -- I think that's fine, as long as we understand what "stable" 14:18:08 14:18:09

is in the context here, and as we looked at before in Column 1 starting at line 21, it says, "increased stability," and there are examples, and I think you're right. They meant probably "be lyophilized," so maybe you said "lyophilizable," yeah. 14:18:15 14:18:18 14:18:22 14:18:27 14:18:28 14:18:33

Q. Yes. The abstract says "lyophilizable," and then this is kind of a typo where it just says "lyophilize" in Column 1. 14:18:45 14:18:46 14:18:49 14:18:52

A. Yeah. 14:18:52

Q. So I was reading from the abstract when I said that. 14:18:53 14:18:55

A. Oh, oh, okay. Let me just look at it for a second. 14:18:59 14:19:03

(Witness reviews document.) 14:19:06

Yeah, thank you. 14:19:06

Q. Okay. And in Column 1 it says, "The lyophilizable formulations can be reconstituted for intravitreal administration," correct? 14:19:08 14:19:11 14:19:18 14:19:21

A. Yes, lines 22 and 23, yes. 14:19:29

Q. Okay. So you would -- I think you maybe already have done this, but you agree then that Furfine is teaching a range of formulations from 1 to 100 mgs per mL of aflibercept suitable for ophthalmic use in intravitreal injection, correct? 14:19:50 14:19:53 14:19:55 14:20:00 14:20:06 14:20:11

MS. KAYALI: Objection. Mischaracterizes prior testimony. 14:20:20 14:20:22

A. I mean, we were talking about the claims, but I -- but I agree. In Column 2, as you correctly read, it comprises 1 to 100 milligrams per milliliter of the VEGF specific fusion protein, other components, it teaches. And I agree it's a liquid ophthalmic formulation that can be injected intravitreally. 14:20:38 14:20:41 14:20:53 14:20:58 14:21:00 14:21:06 14:21:10 14:21:14

BY MR. KANE: 14:21:39

Q. And if you look at Claim 1, a person of ordinary skill reading Furfine and looking at Claim 1 would understand that Furfine's inventors were in possession of Claim 1's 100 mg per mL formulation of aflibercept, 14:21:39 14:21:56 14:21:58 14:22:03 14:22:08

correct? 14:22:27

A. Just so I make sure I heard every 14:22:27

word, could you -- would you please repeat it. 14:22:28

Q. Sure. A person of ordinary skill 14:22:29

reading Furfine and looking at Claim 1 would 14:22:30

understand that Furfine's inventors were in 14:22:33

possession of Claim 1's 100 mg per mL 14:22:36

formulation of aflibercept, correct? 14:22:43

A. I want to be a little careful, only 14:22:54

because -- and I'm -- you asked about 14:23:01

"possession," which I understand is a legal 14:23:04

term, and you're asking about the claims, and 14:23:06

I'm definitely not an attorney. 14:23:10

In answering your question, I can use 14:23:15

the specification, I assume -- 14:23:16

Q. Sure. 14:23:18

A. -- or just -- because you asked just 14:23:18

about the claim. I want to -- 14:23:21

Q. If you'd like to look at the 14:23:22

specification, that's fine. 14:23:24

A. Okay. So your question encompasses 14:23:26

this specification, because I may not 14:23:28

understand it correctly, but I understand when you're -- my thought is when you're looking at possession of a claim, you look at the specification, but you should... 14:23:30 14:23:33 14:23:36 14:23:39

Q. Well, yes. Actually, you can look at -- look at Paragraph 36 of your declaration. 14:23:44 14:23:45 14:23:56

A. Okay. Oh, even better. 14:23:56

Q. So the written description, legal section. 14:24:01 14:24:03

A. Yes, I'm there. 14:24:07

Q. Okay. And you can see there the lawyers have informed you that a patent specification must satisfy the written description requirement, meaning that it conveys with reasonable clarity to a POSA that the inventors actually possess the invention that is claimed as of the priority date sought. Okay? 14:24:08 14:24:12 14:24:15 14:24:17 14:24:19 14:24:22 14:24:25 14:24:38

A. Okay. 14:24:38

Q. So with that definition in mind, I'll ask the question again. 14:24:39 14:24:41

A person looking -- a person of ordinary skill reading Furfine, the patent, and looking at Claim 1 would understand that Furfine's inventors were in possession of Claim 1's 100 mg per mL formulation of aflibercept, correct? 14:24:45 14:24:47 14:24:50 14:24:53 14:24:55 14:25:00

A. Yes, that's correct. Again, that's why I went back, and thank you for pointing me to the legal section, because I understand you're supposed to look at the specification, and I don't -- definitely am not an attorney. 14:25:05 14:25:21 14:25:23 14:25:25 14:25:28

So whatever -- so that -- this question you asked me about the whole document, so -- 14:25:31 14:25:32 14:25:35

Q. Yes, I was asking about the whole document. 14:25:37 14:25:38

A. Yeah. So yes, I mean, I discuss this in my Paragraph 59. There's some "however," but as far as just looking at Furfine, yes. 14:25:38 14:25:41 14:25:44

Q. Okay. Does the -- you have -- you mentioned the "however" statement in Furfine -- or in your Paragraph 59. 14:25:57 14:25:59 14:26:02

Does that -- is there something that changes your answer? 14:26:05 14:26:09

MS. KAYALI: Objection. Vague. 14:26:15

A. Oh, no. I -- well, that is part of my answer. I just wanted to -- I understand we're just looking at Furfine, but I also understand it's certainly in the context of this PGR involving the '036. 14:26:15 14:26:25 14:26:29 14:26:32 14:26:35

So I just wanted to put that pin in with respect to the '036, which I didn't explicitly say, and -- but if we're just looking at Furfine, yes. But I think as -- it's -- in other words -- I see you kind of shook your head. 14:26:40 14:26:45 14:26:50 14:26:56 14:27:00 14:27:04

So, in other words, I understand Furfine is being used as a prior art reference for the '036, and I want to make sure that my answer -- the direct answer to your question is not somehow used in a different context with respect to the '036. That's why I include in this paragraph a few other sentences. 14:27:06 14:27:07 14:27:10 14:27:15 14:27:19 14:27:24 14:27:27 14:27:32

But as far as just -- a few other sentences that connect Furfine to the '036 from the standpoint of the analysis. If we're just looking at the 261 Furfine, then yes. I just want to make sure you don't, like, somehow say, okay, I'm addressing the '036 with respect to that. 14:27:32 14:27:34 14:27:41 14:27:43 14:27:47 14:27:49 14:27:53

I'm just looking at Furfine, that's all. That's the reason why I referred to that full paragraph. 14:27:54 14:27:56 14:27:58

BY MR. KANE: 14:28:01

Q. Okay. I understand. And your answer of -- so the transcript seems a little jumbly. I know it's a -- it's rough at this point, but let me ask the question again just to make sure it's clean and we know what we've got here. 14:28:01 14:28:07 14:29:01 14:29:06 14:29:08 14:29:10

So a person of ordinary skill looking at Furfine and looking at Claim 1 of Furfine would understand that Furfine's inventors were in possession of Claim 1's 100 mg per mL formulation of aflibercept, correct? 14:29:16 14:29:18 14:29:23 14:29:27 14:29:35

A. Yes, that's correct with respect to Furfine, I just wanted to say; but it's not the full story with respect to the '036 patent, because I know it's being used as a prior art reference. 14:30:06 14:30:11 14:30:15 14:30:19 14:30:21

But if we're just talking Furfine, then I say affirmative, yes. 14:30:22 14:30:26

Q. Okay. Thank you. 14:30:29

Dr. Trout, I'm going to hand you what's been marked Alvotech 1006, which is the Dix patent. 14:31:19 14:31:21 14:31:26

A. Okay. 14:31:27

Q. And this is another patent that is being used as prior art against the '036, and which you analyzed in your work on this matter, correct? 14:31:29 14:31:36 14:31:39 14:31:41

A. Yes. 14:31:51

Q. Okay. Let's look at -- let's look at Claim 1. 14:32:08 14:32:10

Well, actually, let's go back to the front. I'm sorry. 14:32:17 14:32:20

So again, you can see the title here 14:32:22

is "Stable Liquid VEGF Antagonist Formulations"? 14:32:24 14:32:29

A. Yes. 14:32:34

Q. Okay. And this is another Regeneron patent? 14:32:37 14:32:42

A. Yes. 14:32:48

Q. And in the upper right-hand corner, we see that it issued December 3, 2014? 14:32:50 14:32:51

A. Correct. 14:32:59

Q. And we see that the provisional -- it claims priority to a provisional application filed on March 25, 2005, right? 14:33:00 14:33:02 14:33:05

A. Yes. 14:33:15

Q. Okay. So we'll keep moving the date back when Regeneron started working with aflibercept to our earlier conversation. 14:33:17 14:33:19 14:33:21

And the abstract says -- describes these as, "Formulations of a vascular endothelial growth factor (VEGF). Specific fusion protein antagonists are provided, including a prelyophilized formulation, a reconstituted lyophilized formulation, and a 14:33:36 14:33:37 14:33:43 14:33:49 14:33:52 14:33:56

stable liquid formulation," correct? 14:33:59

A. Yes. It continues, but yes, that's 14:34:04

the first sentence. 14:34:09

Q. Yes. And then it continues to say, 14:34:10

"Preferably the fusion protein has the 14:34:12

sequence of SEQ ID NO:4," right? 14:34:13

A. Yes. 14:34:21

Q. And SEQ ID NO:4 is aflibercept? 14:34:24

A. I'm pretty sure it is. I didn't do 14:34:40

the direct comparison, but I think it's the 14:34:43

same Sequence ID:4, and that's aflibercept. 14:34:45

Yeah, that's my understanding. Happy to go 14:34:48

with that. 14:34:51

Q. All right. So let's look at -- let's 14:34:52

look at Claim 1 then. 14:34:53

This talks about, "A stable liquid 14:35:01

formulation comprising 100 mgs per mL of a 14:35:02

VEGF antagonist, which is a dimer comprising 14:35:07

two identical polypeptides comprising amino 14:35:12

acids 27 to 457-457 [sic] of SEQ ID NO:4, 14:35:18

20 millimolar histidine, 3 percent 14:35:31

polyethylene glycol (PEG) 3350 with W/V, 14:35:38

5 percent sucrose W/V, and 1.5 percent glycine W/V, at a pH of 6.3 to 6.5," correct? 14:35:50 14:35:56

A. Yes, I think that's what you read. 14:36:05

Q. Okay. And so similar to the previous -- the Furfine patent, a person of ordinary skill reading the '316 patent disclosure and looking at Claim 1 would understand that the inventors possessed the 100 mg per mL formulation of aflibercept in their claim? 14:36:23 14:36:24 14:36:31 14:36:33 14:36:38 14:36:46 14:36:54

A. Well, I think that's -- I would say that -- strike the "think." 14:37:11 14:37:14

I would say that's correct. But it's very important to note that this is not an ophthalmic formulation, and as I say -- so it's very different from the Furfine that we just discussed, and as I say, I literally say this in my second sentence -- 14:37:17 14:37:19 14:37:23 14:37:28 14:37:31 14:37:35

Q. Where are you reading? 14:37:41

A. Sorry, I haven't -- it's page 30, Paragraph 60, which is the beginning of the Dix section. 14:37:42 14:37:48 14:37:52

"Unlike Furfine, Dix is not directed to intravitreal or ophthalmic use. Rather, Dix is directed to VEGF antagonist formulations for cancer treatments." 14:37:53 14:37:56 14:38:00 14:38:04

So I just want to make it clear, Dix possesses a formulation, but it's not for ophthalmics. 14:38:10 14:38:13 14:38:16

Q. Looking at the formulation, is there some component in that formulation that would make it unsuitable for ophthalmics? 14:38:23 14:38:25 14:38:29

A. (Witness reviews document.) 14:39:00

Well, I think the concern with reading Dix, as I discuss here, is the teachings of the examples are a high level of sucrose, and the degree of degradation of the 100 mgs per mL is pretty high. 14:39:17 14:39:20 14:39:31 14:39:39 14:39:50

For example -- well, Example 3 for Tables 5 and 6, and I think the skilled person would be concerned about particulates and other things from Dix which, again, is not contemplating ophthalmic formulations. 14:39:52 14:39:55 14:40:01 14:40:05 14:40:10

Q. Well, so I guess, first of all, 14:40:26

Claim 1 has 5 percent sucrose weight volume, correct? 14:40:27 14:40:30

A. Correct, and other -- other components. 14:40:40 14:40:43

Q. But -- and that's not -- 5 percent sucrose is not an amount that would make the formulation unsuitable for ophthalmic use, correct? 14:40:44 14:40:46 14:40:51 14:40:55

MS. KAYALI: Sorry. Counsel, could I ask you to speak up? I'm just not -- like, suitable versus un, I just don't hear the "un." 14:40:56 14:40:57 14:40:59 14:41:01

MR. KANE: Gotcha. 14:41:03

BY MR. KANE: 14:41:03

Q. Would a 5 percent sucrose excipient make a formulation unsuitable for ophthalmic use? 14:41:03 14:41:05 14:41:09

A. Not necessarily of itself, but when the skilled person looks at Dix -- and I discuss exactly in here that Dix does not -- the same paragraph, page 31, the end sentence, "Dix does not disclose any formulation 14:41:17 14:41:21 14:41:23 14:41:31 14:41:36

suitable for intravitreal administration." 14:41:39

That's how the skilled person would 14:41:42

read this, and when one looks at the 14:41:43

specification as a whole, as I understand 14:41:47

one's supposed to do. 14:41:50

Q. Well, what makes it unsuitable for 14:41:51

ophthalmic use? That was the question I'm 14:41:55

asking. 14:41:57

And you pointed to the sucrose, and 14:42:00

have you now established that the claimed 14:42:05

amount of sucrose does not make it unsuitable, 14:42:06

correct? 14:42:14

A. Just to be correct in the -- I think 14:42:14

of itself it's fine, but I think you 14:42:18

pointed -- I don't think I -- you pointed, you 14:42:21

asked me about that, right? 14:42:23

Q. Well, just to -- I brought it up 14:42:24

because you said looking at examples in Dix, 14:42:26

there are high levels of sucrose in many of 14:42:32

those that would make them unsuitable for 14:42:35

ophthalmic use. 14:42:40

A. I mean, I think you could point that 14:42:44

out. That's not what I said, though. 14:42:46

I was -- I pointed the higher degrees 14:42:49

of degradation, which would concern the 14:42:52

skilled person about particulates and whatnot. 14:42:56

I think that's what I said. 14:43:01

And the reason is because the context 14:43:05

is much different here, and again, that's why 14:43:07

I explicitly say in that sentence on page 31, 14:43:12

which I read before, "Dix does not disclose 14:43:17

any formulation suitable for intravitreal 14:43:20

administration." 14:43:23

It's not contemplated in Dix. It's 14:43:25

for oncology applications. 14:43:26

Q. Okay. So you did mention sucrose in 14:43:29

your example earlier, but that's fine, okay. 14:43:33

So again, looking at Claim 1, what -- 14:43:42

what makes a formulation falling within the 14:43:56

scope of that claim unsuitable for ophthalmic 14:43:59

use? 14:44:01

MS. KAYALI: Objection. Vague. 14:44:09

Calls for a legal conclusion. 14:44:09

A. I mean, you're kind of twisting around 14:44:28

the analysis here. 14:44:30

The point is, I guess if you want me 14:44:35

to answer the question directly and then 14:44:38

explain, it's not contemplated in Dix to be 14:44:42

suitable for ophthalmic administration, and so 14:44:46

that's why I say in that same beginning of the 14:44:52

sentence, "Dix does not disclose any 14:44:55

formulation suitable for intravitreal 14:44:58

administration." 14:45:01

BY MR. KANE: 14:45:03

Q. And -- 14:45:03

A. And degradation is one of the reasons, 14:45:05

and I think -- you or I brought up, but I 14:45:06

think we all agree that the sucrose in the 14:45:10

examples is way too high, which I think is 14:45:13

another -- perhaps fine for oncology, but not 14:45:15

for intravitreal administration, and that's 14:45:19

just another reason -- I mean, I have more 14:45:22

analyses, but that's another reason why it -- 14:45:25

what's contemplated is unsuitable. 14:45:30

I would just say it's -- it doesn't 14:45:32

disclose any formulation suitable for 14:45:34

intravitreal administration.

Q. And I guess -- that's where I'm struggling when you say "not suitable."

You're saying it discloses formulations that are not suitable or does not -- excuse me.

You're saying Dix nowhere teaches or suggests that --

A. Oh, I'm sorry. I'm -- are you in the previous page?

Q. Which page are you on?

A. I can go to whatever.

Q. You're right. It's page 31, the last sentence, right?

"Dix does not disclose any formulation suitable for intravitreal administration."

Is that what you're pointing at?

A. Yes.

Q. Okay. And when you say, "does not disclose a formulation suitable for intravitreal administration," what are you relying on?

MS. KAYALI: Objection. Vague. 14:46:42

A. I mean, rely -- I'm talking about the examples here and the fact that Dix -- I don't think anyone disagrees, but I think, as I say on page 30, the second sentence, we talk about this, "Unlike Furfine, Dix is not directed to intravitreal or ophthalmic use. Rather, Dix is directed to VEGF antagonist formulations for cancer treatment." 14:46:43 14:46:47 14:46:54 14:46:56 14:47:04 14:47:09 14:47:12 14:47:15

So it's not contemplating intravitreal administration. 14:47:17 14:47:21

BY MR. KANE: 14:47:26

Q. So just the fact that it's contemplated for cancer makes it not suitable for intravitreal use? 14:47:26 14:47:27 14:47:31

MS. KAYALI: Objection. Mischaracterizes testimony. Lacks foundation. 14:47:34 14:47:35

A. No, also the examples that I discussed. All the examples have high degradation -- well, not all of them. I say some of the examples have high degradation, which I think would be a concern; but more 14:47:41 14:47:43 14:47:48 14:47:50 14:47:52

importantly, the -- that they're all at high sucrose levels, 20 percent, all, as I say, disclose any formulation. I'm talking about the examples are all at 20 percent sucrose. They're high sucrose. 14:47:55 14:48:05 14:48:09 14:48:12 14:48:15

BY MR. KANE: 14:48:19

Q. But the claim is not high sucrose, right? We've established that. 14:48:19 14:48:22

MS. KAYALI: Is that a question? 14:48:26

BY MR. KANE: 14:48:28

Q. Haven't we -- have we established that the claim is not a high sucrose amount? 14:48:28 14:48:30

A. The claim is a lower sucrose amount than what's in the examples. Correct. 14:48:35 14:48:38

Q. So that doesn't make it -- again, I'll start over. 14:48:47 14:48:54

5 percent sucrose level in the Dix formulation does not make it unsuitable for intravitreal administration, agree? 14:48:55 14:48:57 14:49:02

A. It's not just the 5 percent. It's -- if one reads the full teaching, the fact that the focus of Dix is on cancer treatment. It 14:49:15 14:49:18 14:49:25

doesn't talk about intravitreal administration, and it does not disclose any formulation suitable for intravitreal administration. 14:49:32 14:49:35 14:49:39 14:49:43

Q. It doesn't use the words "suitable for intravitreal administration," correct? 14:49:43 14:49:48

MS. KAYALI: Objection. Vague. 14:49:50

A. I mean, I think that's correct. But that's not the reason. It's -- the reason is as I've been explaining. Well, I guess it's part of the reason. I should -- sorry, to be clear, but the main reason is what I've been explaining. I mean, of course, that's part of it. 14:49:56 14:49:59 14:50:04 14:50:16 14:50:18 14:50:21 14:50:24

BY MR. KANE: 14:50:27

Q. And when you say there's degradation, can you point me to what you're looking at. 14:50:27 14:50:29

A. Yeah, I was -- so, again, it's reading of the Dix as a whole. What I was pointing to was Example 3. That's the example with the 100 mgs per mL. 14:50:51 14:50:55 14:50:58 14:51:06

It's in Column 9, and you can see, and 14:51:08

these are -- these formulations, the 20 percent sucrose, you can see at zero months, there's already significant -- significantly less than 100 of percent VEG native configuration, and that's with the 20 percent sucrose. So one wouldn't want to use it for intravitreal injection anyway. But that's what I was referring to in terms of the, we can call it, native configuration percentage. 14:51:11 14:51:14 14:51:17 14:51:22 14:51:29 14:51:33 14:51:40 14:51:42 14:51:49

MS. KAYALI: Counsel, I'm sorry to interrupt you. I just would appreciate a restroom break, if you wouldn't mind. 14:52:47 14:52:47 14:52:50

MR. KANE: Sure. 14:52:51

MS. KAYALI: Thank you. 14:52:52

THE VIDEOGRAPHER: This is the end of Media No. 4. We are going off the record. The time is 2:53 p.m. 14:52:53 14:52:56 14:52:58

14:53:00

(Recess taken from 2:53 p.m. to 2:59 p.m.) 14:53:00 14:53:00 14:53:00

14:53:33

THE VIDEOGRAPHER: This is the 14:53:34

beginning of Media No. 5. We are going back on the record. The time is 3:00 p.m. 14:59:25 14:59:28

BY MR. KANE: 14:59:32

Q. Dr. Trout, let's look at Example 5 in Dix. It starts at the bottom of Column 10 of the patent. 14:59:33 14:59:35 14:59:45

A. Okay. I'm actually already open to that page. 14:59:47 14:59:49

Q. And you see it's entitled, "Stability and activity of lyophilized and liquid"? 14:59:53 14:59:54

A. Yes. 15:00:00

Q. And it starts off by saying, "The stability of a reconstituted lyophilized formulation was determined over a six-month period," correct? 15:00:07 15:00:09 15:00:11 15:00:16

A. Yes. 15:00:18

Q. And then it has the prelyophilized formulation, and it lists that out, correct? 15:00:19 15:00:23

A. Yes. 15:00:27

Q. And then if you turn to Column 11. 15:00:28

A. Yes. 15:00:47

Q. Excuse me. You have to go back to 10. 15:00:48

I'm sorry. I thought it -- we're back on Column 10. I'm sorry. 15:00:50 15:00:53

A. Okay. I'm back. 15:00:55

Q. The second line from the bottom, it says, "After lyophilization, the reconstituted formulation contained 20 millimolar histidine, 3 percent PEG 3350, 5 percent sucrose, 1.5 percent glycine and 100 mg per mL of VEGF trap (SEQ ID NO:4)." 15:00:57 15:00:59 15:01:05 15:01:10 15:01:16 15:01:22

Do you see that? 15:01:27

A. Yes. 15:01:27

Q. And then it says, "The results are shown in Table 8, stability of VEGF trap lyophilized formulation stored at 5 degrees C." 15:01:28 15:01:30 15:01:36 15:01:39

Do you see that? 15:01:43

A. Yes. 15:01:43

Q. And that, "Formulation has native confirmation ranging from 98.7 to 98.2 at various measurement points between zero and six months." 15:01:45 15:01:46 15:01:57 15:01:59

Do you see that? 15:02:01

A. Yes. 15:02:07

Q. So not all the examples had 20 percent sucrose, correct? 15:02:10 15:02:13

A. Yes. That -- that's correct. And that's -- so this example is part of what I analyzed. 15:02:36 15:02:39 15:02:43

I'm glad you brought that up because I explicitly say, and I think this is the point about the claim, the very bottom of page 30 of my declaration, under the Dix section, Dix also discloses lyophilized formulations that are reconstituted to 100 mgs per mL, but these formulations are stored as lyophilized solids, not as ready-to-use liquid formulations like the '036 formulations. 15:02:44 15:02:46 15:02:49 15:02:54 15:03:00 15:03:05 15:03:10 15:03:15 15:03:20

And remember earlier, I guess you read correctly from the abstract and correctly corrected from the specification that these are reconstituted -- well, they're lyophilizable or reconstituted lyophilized formulation. So that's what's -- that's what's contemplated here, unlike the '036. 15:03:24 15:03:26 15:03:30 15:03:31 15:03:35 15:03:39 15:03:42

Q. You're saying -- the '036 patent claims do not cover lyophilized formulations? 15:03:48 15:03:53 15:03:55

MS. KAYALI: Objection. Calls for a legal conclusion. 15:03:57 15:04:00

A. Well, just to be clear, I'm not sure if that's the question you wanted to ask, but the answer to that question is no, they do not cover a lyophilized formulation. 15:04:07 15:04:29 15:04:31 15:04:37

BY MR. KANE: 15:04:38

Q. Why not? 15:04:38

A. I mean, you can go through them. So I'm back to the '036 now. 15:04:45 15:04:53

Q. Correct. 15:04:57

A. Claim 1, there's no -- oh, yeah, there are line numbers. So approximately line 59, it says, "aqueous pharmaceutical formulation." 15:04:57 15:05:03 15:05:07

Q. Correct. 15:05:12

A. "An aqueous" -- good, you see it. 15:05:14

"An aqueous pharmaceutical formulation is not lyophilized pharmaceutical formulation which is a solid." 15:05:16 15:05:19 15:05:23

And then if we go through the various dependent claims -- well, it doesn't really matter because the independent does not cover the lyophilized, and as I understand, dependent claims have additional limitations. 15:05:26 15:05:32 15:05:36 15:05:41 15:05:48

If we look at Claim 31, lines -- I think it's 20 to 21, it also says, "an aqueous pharmaceutical formulation." 15:05:50 15:05:56 15:06:01

"An aqueous pharmaceutical formulation is a liquid." 15:06:04 15:06:05

You asked about lyophilized. Lyophilized are solid formulations. 15:06:08 15:06:09

And then finally, with Claim 35, approximately line 32, it also says, "An aqueous pharmaceutical formulation, similarly an aqueous pharmaceutical formulation is a liquid." 15:06:13 15:06:17 15:06:22 15:06:28 15:06:31

A lyophilized is a solid. So it wouldn't cover lyophilized, and it's the same for the dependent claims, therefore, of -- and I apologize, 31 also depends on 1. 35 is independent. So it would also have to do with 15:06:33 15:06:36 15:06:37 15:06:43 15:06:48

the dependent claims for Claim 35. 15:06:53

Q. What about the reconstituted 15:06:58

lyophilized formulation? 15:07:01

A. Similarly, for the reconstituted 15:07:08

lyophilized formulation. So if we go through, 15:07:11

if we're reading the specification as a whole, 15:07:17

it's clearly about liquid formulations as 15:07:22

liquids, so not lyophilized reconstituted 15:07:27

formulations. And that is something that's a 15:07:33

significant departure from Dix also. 15:07:39

Q. But what's a significant departure 15:07:49

from Dix also? 15:07:51

A. Oh, well, it's in the abstract, but I 15:07:57

thought there was someplace you also pointed 15:08:34

me to in the -- in the other -- the main part 15:08:37

of the specification, but I think -- anyway, I 15:08:41

think the example 5 that we referred to is an 15:08:46

example which is the formulation of Claim 1 of 15:08:56

the Dix patent, the '316, and that's the -- 15:09:03

that's a liquid formulation. That's -- that's 15:09:07

reconstituted lyo in this case. 15:09:11

The departure is the way Dix describes 15:09:14

its formulations includes this reconstituted lyo -- lyophilized, apology, we're used to saying the shorthand -- reconstituted lyophilized formulations, whereas the '036 is discussing liquid formulation, so formulations that stay liquids, that are not lyophilized before. 15:09:18 15:09:22 15:09:26 15:09:29 15:09:36 15:09:42 15:09:45

Q. So you are interpreting Claim 1 to not cover -- Claim 1 of '036 to not cover reconstituted lyophilized formulations? 15:10:00 15:10:09 15:10:16

MS. KAYALI: Objection. Calls for a legal conclusion. Foundation. 15:10:21 15:10:24

A. I mean, I don't -- my reading of the '036 patent, as a skilled person, I guess you could say it's me, but through the eyes of the skilled person number 2, the formulator, is that this is not a reconstituted liquid formulation. So it's -- it's not reconstituted into a liquid. It's just a liquid formulation. 15:10:32 15:10:50 15:10:55 15:11:00 15:11:05 15:11:12 15:11:16 15:11:20

BY MR. KANE: 15:11:24

Q. Is there any -- do you recall that 15:11:24

when we looked at Furfine, the other Regeneron patent, the '261 patent -- 15:11:25 15:11:31

A. Okay. I've got -- 15:11:34

Q. Go to Claim 1 -- excuse me. Column 1. Starting at line 21, it says, "The invention includes liquid pharmaceutical formulations having increased stability, as well as formulations that may be lyophilized and reconstituted for intravitreal administration." 15:11:36 15:11:45 15:11:49 15:11:53 15:11:55 15:11:59 15:12:01

Right? 15:12:04

A. Yes, and I agree with your grammatical correction. 15:12:08 15:12:11

Q. And so there's no -- let me start over. 15:12:12 15:12:20

Because a formulation is a reconstituted lyophilized formulation does not mean that it is not suitable for intravitreal administration, correct? 15:12:22 15:12:23 15:12:28 15:12:33

MS. KAYALI: Objection. Foundation. Scope. 15:12:38 15:12:38

A. I mean, you're asking a very 15:12:48

high-level question. So, I mean, I guess in theory, something can be -- could be -- I think there would be concerns. The point is that if you look at the examples in Furfine, there are examples of liquid formulations that have never been lyophilized. 15:12:50 15:12:55 15:13:01 15:13:05 15:13:11 15:13:15

Example 8 is an example of a lyophilized formulation. The claims, as I think a skilled person would understand them, are to the liquid formulations. 15:13:20 15:13:22 15:13:32 15:13:34

With the Dix, the claim -- well, we talked about Claim 1 is explicit to a reconstituted lyophilized formulation. It's right in the specification. 15:13:38 15:13:40 15:13:45 15:13:48

BY MR. KANE: 15:13:56

Q. The question I was asking was, would you agree with me that Furfine teaches that it's possible to make a lyophilized formulation reconstituted and injected intravitreally? 15:13:56 15:13:59 15:14:01 15:14:08 15:14:14

MS. KAYALI: Objection. Vague. 15:14:19

A. Again, I agree, we read it. It 15:14:27

teaches that at a high level. I think reading Furfine will tell you that the claims are to liquid formulations; in Furfine, not Dix. 15:14:51 15:14:56 15:15:03

I mean -- let me be clear. Liquid that hadn't been reconstituted, hadn't previously been lyophilized. And Dix has the example of lyophilized formulations. 15:15:13 15:15:16 15:15:19 15:15:21

BY MR. KANE: 15:15:40

Q. Well, both Dix and Furfine have examples of lyophilized formulations, right? 15:15:40 15:15:42

A. Yes. I mean, Furfine has examples too, right. 15:15:46 15:15:48

Q. Right? 15:15:49

A. Yes. 15:15:49

Q. And Furfine, which has lyophilized formulations, the title of the patent is "VEGF antagonist formulations suitable" -- 15:15:59 15:16:02 15:16:05

A. Wait, wait, let me get -- 15:16:08

Q. Sorry. 15:16:10

A. Okay. I'm at -- we're in Furfine? 15:16:10

Q. We're in Furfine. 15:16:13

A. Okay. 15:16:15

Q. First of all, Furfine has both liquid formulations and lyophilized formulations, correct? 15:16:15 15:16:19 15:16:28

MS. KAYALI: Objection. Vague. You can answer. 15:16:28 15:16:29

A. I mean, by having it, it discusses both. 15:16:29 15:16:32

BY MR. KANE: 15:16:34

Q. It has examples of both? 15:16:34

MS. KAYALI: I'm sorry. It's hard to hear you. 15:16:36 15:16:37

BY MR. KANE: 15:16:38

Q. It has examples of both? 15:16:38

MS. KAYALI: Thank you. 15:16:40

A. Yes. 15:16:42

BY MR. KANE: 15:16:43

Q. And the title of Furfine is, "VEGF antagonist formulation suitable for intravitreal administration," right? 15:16:43 15:16:46 15:16:49

A. Yes. 15:16:51

Q. So Furfine's liquid formulations are suitable for intravitreal administration? 15:16:59 15:17:01

MS. KAYALI: Objection. 15:17:05

BY MR. KANE: 15:17:11

Q. Correct? 15:17:11

A. Yes. 15:17:11

Q. And Furfine's reconstituted lyophilized formulations are suitable for intravitreal administration, correct? 15:17:13 15:17:17 15:17:21

A. I mean, it's certainly -- Furfine certainly has this high-level statement that we've been to many times, and so it certainly contemplates Column 1, line 22, formulations that may be lyophilized with the correction and reconstituted for intravitreal administration. So yes, they can be for intravitreal administration. 15:17:40 15:17:41 15:17:47 15:17:52 15:17:55 15:17:59 15:18:02 15:18:06

Q. If we look at the '036 patent again, the claims, Claim 1. 15:18:40 15:18:44

A. Okay. 15:18:53

Q. As I understand it, the reason that you say Claim 1 does not cover a reconstituted lyophilized formulation is because it says "aqueous pharmaceutical formulation"? 15:19:08 15:19:10 15:19:17 15:19:20

MS. KAYALI: Objection. That misstates prior testimony. 15:19:28

A. No, it's not -- it's not just because of that. That -- that's the reason it's not a solid lyophilized formulation. I think -- 15:19:05 15:19:08 15:19:12

BY MR. KANE: 15:20:16

Q. Why is it not a reconstituted -- 15:20:16

MS. KAYALI: Sorry. 15:20:18

Dr. Trout, were you done with your answer? 15:20:19 15:20:20

THE WITNESS: No, I wasn't done with my answer. 15:20:21 15:20:21

BY MR. KANE: 15:20:21

Q. I'm sorry. I thought you were done. 15:20:21

A. But maybe I'm going to answer the same question. 15:20:23 15:20:26

So I think reading the specification and understanding the specification -- sorry, understanding the claim in light of the specification, would tell the skilled person that this is not a reconstituted lyophilized formulation. It's an aqueous pharmaceutical 15:20:27 15:20:30 15:20:34 15:20:36 15:20:39 15:20:45

formulation. At least that's what's discussed in the specification. 15:20:48 15:20:53

Q. Okay. So it is -- and the Claim 1 uses that phrase "aqueous pharmaceutical formulation," correct? 15:20:58 15:21:00 15:21:02

A. Yes. 15:21:07

Q. So that -- I thought I asked you if that was the phrase that distinguished Claim 1 of '036 from a reconstituted lyophilized formulation, and you said no. 15:21:09 15:21:13 15:21:16 15:21:19

A. Correct, and then I continued the answer. 15:21:28 15:21:30

Q. Well, okay. 15:21:33

A. Maybe I -- 15:21:35

Q. Can you give me again the reason? Why does Claim 1 not cover a -- what language in Claim 1 tells you that it does not cover a reconstituted lyophilized formulation? 15:21:35 15:21:37 15:21:46 15:21:53

A. So again, it's reading the claim in light of the specification. The '036 has a different specification than Dix. 15:22:27 15:22:34 15:22:40

And if you look at, for example, the 15:22:43

technical field, which is Column 1, it says, 15:22:49
starting at line 22, "More particularly, 15:22:57
embodiments herein provide liquid 15:23:01
pharmaceutical formulations for intravitreal 15:23:04
administration where the formulations include 15:23:08
more than 40 mgs per mL of VEGF receptor 15:23:09
fusion protein," and it continues, and 15:23:15
there's a -- except there's a focus on 15:23:18
viscosity and stability. 15:23:20
And then if one reads the 15:23:23
specification, you see the focus is on liquid 15:23:24
formulations, per se, not reconstituted ones. 15:23:29
Q. Again, so what language in the claim, 15:23:34
though, are you pointing to? 15:23:36
A. I mean, I guess if -- it is "aqueous 15:23:49
pharmaceutical formulation," but read in light 15:23:57
of the specification -- 15:24:00
Q. Okay. 15:24:02
A. -- as I've been saying. 15:24:04
Q. Let's look at Column 14 of the 15:24:06
specification. 15:24:16
A. Okay. I'm there. 15:24:18

Q. Starting at line 6, there's a definition of "pharmaceutical formulation." 15:24:19 15:24:22

"Herein refers to formulations, including pharmaceutically acceptable carriers, e.g., used to administer VEGF receptor proteins (e.g., aflibercept or conbercept -- conbercept)" c-o-n-b-e-r-c-e-p-t, "to a subject for a therapeutic medicinal use." 15:24:25 15:24:28 15:24:31 15:24:40 15:24:43 15:24:46 15:24:51

Do you see that? 15:24:53

A. Yes. 15:24:53

Q. Does a reconstituted lyophilized formulation meet that definition? 15:25:00 15:25:02

A. (Witness reviews document.) 15:25:04

At a high level, I guess it could meet that definition. I think it's important to understand how the formulation scientist would read the specification as a whole and interpret the claims in light of the specification. 15:25:58 15:26:01 15:26:05 15:26:09 15:26:12 15:26:13

Q. Okay. And then if you go down a few more lines to about line 18 I guess, it says, 15:26:15 15:26:17

"The term 'aqueous formulation' refers to a formulation which includes water." 15:26:23 15:26:27

Do you see that? 15:26:33

A. Yes. 15:26:33

Q. Does a reconstituted lyophilized formulation include water? 15:26:34 15:26:38

A. It does. And that's why I was emphasizing that "aqueous pharmaceutical formulation" in the claims has to be read in the specification as a whole. And that's why I think the skilled person would understand that these claims in the '036 are to liquid formulations within the contents of the examples and the specification as a whole. 15:26:46 15:26:51 15:26:53 15:26:55 15:27:01 15:27:03 15:27:09 15:27:12

Q. And when you say "liquid formulations," you mean to exclude reconstituted lyophilized formulations? 15:27:15 15:27:16 15:27:23

A. That's right. It's a liquid formulation, meaning it's formulated and stays as a liquid as opposed to being freeze-dried. 15:27:26 15:27:31 15:27:34

Q. Dr. Trout, I'm going to hand you what's been marked as Alvotech 1007. 15:27:51 15:27:53

MS. KAYALI: Thank you. 15:27:58

Q. Vitti. 15:27:59

A. Okay. 15:28:00

Q. That's at least how we say it. I don't know how you say it. 15:28:01 15:28:04

And actually, it's a patent application. The publication date was May 26, 2016. 15:28:11 15:28:13 15:28:19

Do you see it on the right side? 15:28:20

A. Yes. 15:28:23

Q. And it's, again, a Regeneron patent application? 15:28:24 15:28:28

A. Yes. 15:28:33

Q. And would you agree with me that this application is disclosing therapies that involve both an Ang-2 inhibitor and a VEGF antagonist? 15:28:42 15:29:01 15:29:07 15:29:11

A. So you said "involve" in your question? 15:29:12 15:29:24

Q. Yes. 15:29:25

A. I mean, I would just stick to the way I characterized it. For example, in my 15:29:26 15:29:29

summary section on page 31, second sentence of Paragraph 62, "Vitti is primarily directed to methods in pharmaceutical formulations for treating vascular eye diseases using combinations of an angiopoietin-2, Ang-2, inhibitor, mAB1, and a VEGF antagonist including aflibercept." 15:29:34 15:29:41 15:29:45 15:29:46 15:29:50 15:29:57 15:30:00

So I used the term "combinations." 15:30:02

Q. Okay. And what do you mean when you -- what do you mean when you use the term "combinations" there? 15:30:05 15:30:05 15:30:06

MS. KAYALI: Dr. Trout, were you finished? 15:30:07 15:30:08

THE WITNESS: Yeah. 15:30:10

A. I just wanted to finish and just say if that's what you mean by "involve," then we mean the same thing. 15:30:10 15:30:11 15:30:13

BY MR. KANE: 15:30:15

Q. What do you mean by "combinations"? 15:30:15

A. Well, if we skip the next two sentences and go to the last full sentence on page 31, what I mean is Vitti's exemplary 15:30:30 15:30:31 15:30:35

formulations contain 40 mgs per mL of aflibercept, in combination with 10 to 120 mgs per mL mAb1, which I talked about before in the previous sentence that I read, and then it continues with the formulation. 15:30:40 15:30:43 15:30:48 15:30:51 15:30:53

Q. So do you mean one formulation with both the Ang-2 inhibitor and the VEGF antagonist? 15:30:58 15:30:59 15:31:04

MS. KAYALI: Objection. Vague. 15:31:12

A. (Witness reviews document.) 15:31:54

I mean, there are certainly coformulations discussed in Vitti, as you explained -- or as you asked. There are also formulations -- well, there are ang- -- sorry, Ang-2 inhibitor formulations, the mAb1 formulations by themselves, which I'm reading to be a coadministration separately, but not a coformulation perhaps. 15:31:54 15:32:00 15:32:07 15:32:13 15:32:17 15:32:20 15:32:25 15:32:30

So I think it's -- it discusses both, but the point is they all have 40 mgs per mL of aflibercept in combination with the Ang-2 inhibitor, whether together but separate 15:32:33 15:32:35 15:32:38 15:32:48

formulations or coformulated. 15:32:54

Q. If you look at Paragraph 88. 15:33:30

A. Of my... 15:33:35

Q. No, sorry, of the application of 15:33:36

Vitti. 15:33:38

Now we're going to have a paragraph 15:33:41

problem, because this has -- instead of 15:33:42

columns and line numbers, it has paragraphs, 15:33:43

so I'll try to be clear. 15:33:46

A. Okay, I'm at Paragraph 88 of Vitti. 15:33:53

Q. You see there that it refers to 15:33:57

combination therapies just above 88? 15:33:59

A. Oh, above. Yes, I see that. 15:34:05

Q. And then the second line says, "As 15:34:08

used herein, the expression 'in combination 15:34:13

with' means the VEGF antagonist is 15:34:16

administered before, after, or concurrent with 15:34:20

the pharmaceutical composition comprising the 15:34:25

anti-Ang-2 antibody." 15:34:28

Do you see that? 15:34:34

A. Yes. 15:34:34

Q. So is that consistent with your use of 15:34:37

"combination" in your declaration as well? 15:34:39

MS. KAYALI: Objection. 15:34:50

Foundation. 15:34:51

A. Yes, I think it's consistent. 15:35:11

BY MR. KANE: 15:35:25

Q. Okay. And Vitti specifically 15:35:25

identifies aflibercept as one of its exemplary 15:35:26

VEGF antagonists, correct? 15:35:30

MS. KAYALI: Objection. 15:35:38

Foundation. 15:35:38

A. You might know where this -- I could 15:35:51

try to -- 15:35:53

BY MR. KANE: 15:35:54

Q. Paragraph 86 of Vitti. 15:35:54

A. Okay. 15:35:56

Q. Look there. 15:35:56

A. (Witness reviews document.) 15:35:58

Yes. Thank you. 15:36:06

It says, "An exemplary VEGF 15:36:08

receptor-based chimeric molecule," and then it 15:36:10

talks -- then it mentions aflibercept, yes. 15:36:16

Q. Okay. So now let's look at Paragraph 15:36:24

127 of Vitti. 15:36:26

A. Okay. 15:36:42

Q. And this is -- the second sentence in that paragraph says, "In certain embodiments, the liquid formulation comprising of 10 to 20 mgs per mL to 120 mgs per mL of anti-Ang-2 antibody, and from 10 mgs per mL to 100 mgs per mL of aflibercept, is comprised in a prefilled syringe and is administered intravitreally in a volume of approximately up to 100 microliters." 15:36:42 15:36:45 15:36:47 15:36:52 15:36:58 15:37:04 15:37:06 15:37:10 15:37:15

Do you see that? 15:37:20

A. I mean, apologies. I think you made a verbal typo again, or misread the last part. 15:37:20 15:37:28

Q. What did I misread? 15:37:48

A. Maybe I'm not... 15:37:50

I mean, here it says -- I'm reading this saying, "volume of approximately up to 500 microliters," is what's written here. 15:37:56 15:38:01 15:38:07

Q. I'm above that. 15:38:11

A. Oh, I apologize. 15:38:12

Q. Yeah, it's the second full sentence, 15:38:15

starts "In certain embodiments." Sorry. 15:38:17

A. Oh, okay, I think I jumped. 15:38:21

Q. You jumped one sentence below me. 15:38:22

A. I apologize. I was following that sentence. 15:38:24 15:38:29

Q. So why don't you read the sentence above to yourself. 15:38:32 15:38:35

A. Okay. 15:38:37

(Witness reviews document.) 15:38:50

Okay, thank you. Sorry about that. Now we're on the same sentence, in addition to the same page. 15:38:50 15:38:52 15:38:55

Q. So that sentence in Vitti teaches the administration of up to 100 mgs per mL of aflibercept intravitreally, correct? 15:38:57 15:39:00 15:39:03

MS. KAYALI: Objection. Foundation. 15:39:09 15:39:10

A. I mean, I agree that's what it says in this sentence. And I think I discuss this, maybe a different paragraph, but I discuss this in -- I mean, a different paragraph in Vitti, which I discuss in my Paragraph 62 on 15:39:40 15:39:45 15:39:49 15:39:51 15:39:54

Vitti. 15:39:58

BY MR. KANE: 15:40:30

Q. So -- but just so your answer is 15:40:30

clear, you agree that this sentence in Vitti 15:40:37

teaches the administration of up to 100 mgs 15:40:39

per mL of aflibercept intravitreally, 15:40:43

correct? 15:40:45

MS. KAYALI: Objection. Asked 15:40:48

and answered, and vague. 15:40:49

A. Maybe I misunderstood your previous 15:41:00

question, because I think you were asking -- 15:41:03

maybe I thought you were asking something 15:41:06

else. 15:41:07

I want to be clear. This is about a 15:41:08

combination. I think it's talking about a 15:41:14

combination, and it does say to 100 milligrams 15:41:18

per milliliter of aflibercept in that 15:41:26

combination. 15:41:29

And I, again, discuss -- I think it's 15:41:31

100 milligrams per milliliter disclosure of 15:41:35

aflibercept -- oh, I apologize again. I 15:41:41

think -- I said it was a different paragraph, 15:41:47

but it is exactly that paragraph. I apologize. 15:41:49 15:41:51

I discuss this exactly in the sentence, 62. I hope that clarifies it. I can restate it if it doesn't, but that's what I was referring to in Paragraph 62, that sentence which is -- which is a combination. 15:41:51 15:41:53 15:41:57 15:41:59 15:42:03

BY MR. KANE: 15:42:08

Q. Okay. I understand that, but that doesn't quite answer my question, I don't think. 15:42:08 15:42:10 15:42:13

Are you saying -- all right. So let me ask this question, you're saying then that sentence teaches administering the combination or -- let me start over. 15:42:14 15:42:18 15:42:25 15:42:32

That sentence teaches delivering 100 -- up to 100 milligrams per milliliter of aflibercept in combination intravitreally? 15:42:34 15:42:36 15:42:41

MS. KAYALI: Objection. Foundation. 15:42:52 15:43:11

A. I think what you read is a combination, and the patent as a whole is -- 15:43:11 15:43:15

discusses combinations. The focus is on the anti-Ang-2 combined with VEGF proteins, and so this teaches a combination. 15:43:25 15:43:29 15:43:38

And again, as I have in my -- I discuss exactly this paragraph in my -- my Paragraph 62 regarding the 100 milligrams per milliliter of aflibercept, and in other places, but this is just the summary. 15:43:43 15:43:46 15:43:51 15:43:59 15:44:01

BY MR. KANE: 15:44:19

Q. You would agree with me there are other places in the patent application that describe delivering the VEGF antagonist aflibercept separately from the Ang-2 inhibitor, correct? 15:44:19 15:44:20 15:44:26 15:44:30 15:44:32

MS. KAYALI: Objection. Foundation. 15:44:35 15:44:40

A. I mean, you're talking about Vitti still? 15:44:40 15:44:42

BY MR. KANE: 15:44:43

Q. Yes. 15:44:43

A. Well -- 15:44:45

Q. Let's look at -- let's look at 15:44:46

Paragraph 18. 15:44:47

A. Sorry. The number? 15:44:48

Q. Paragraph 18. 15:44:50

A. One eight? 15:44:51

Q. Yes. 15:44:51

A. Okay, thank you. 15:44:52

MS. KAYALI: Sorry. Counsel, 18 of Vitti is what we're looking at? 15:44:53 15:44:54

MR. KANE: Yes. 15:44:56

MS. KAYALI: Okay, thank you. 15:44:57

THE WITNESS: Okay. 15:45:08

BY MR. KANE: 15:45:09

Q. All right. So let's walk through it. 15:45:09

It says, "In certain embodiments, the Ang-2 inhibitor is administered as a coformulation with a VEGF antagonist," right, first sentence? 15:45:10 15:45:11 15:45:14 15:45:19

A. Yes. 15:45:21

Q. Okay. Then the next sentence says, "In certain embodiments the Ang-2 inhibitor alone or in combination with the VEGF antagonist is intravitreally administered to a 15:45:33 15:45:34 15:45:38 15:45:41

subject in need thereof," correct? 15:45:44

A. Yes. 15:45:53

Q. Okay. The next one is, "In alternate embodiments, the Ang-2 inhibitor is administered intravenously or subcutaneously." 15:45:53 15:45:58 15:46:00

Do you see that? 15:46:10

A. Yes. 15:46:10

Q. And the next one is, "In certain embodiments, the Ang-2 inhibitor is administrated [sic] intravenously or subcutaneously in combination with the VEGF antagonist, wherein the VEGF antagonist is administered intravitreally." 15:46:12 15:46:13 15:46:17 15:46:19 15:46:23 15:46:25

Do you see that? 15:46:29

A. Yes. I think you may have said "administrated," but it's "administered," but yes, it's there. 15:46:29 15:46:38 15:46:40

Q. And so there, for instance, is an example where the VEGF antagonist is administered intravitreally separate from the Ang-2 inhibitor, right? 15:46:45 15:46:48 15:46:51 15:46:54

A. The route of administration of the 15:47:11

Ang-2 inhibitor and the VEGF antagonist, those routes are different, but it explicitly says that they're administered in combination. 15:47:22 15:47:27 15:47:32

Q. Right, I guess. But I'm just saying, that sentence describes a route of an -- a route of administration of a VEGF antagonist intravitreally without any Ang-2 inhibitor intravitreally? 15:47:40 15:47:41 15:47:47 15:47:51 15:47:58

MS. KAYALI: Objection. Vague. 15:48:01

A. If I understood your question, I think it's correct, because the Ang-2 inhibitor is administered intravenously or subcutaneously, but the point here is that Vitti -- I mean, Vitti is really about combinations, with a focus on the anti-Ang-2 or the Ang-2 inhibitor. 15:48:20 15:48:24 15:48:26 15:48:32 15:48:39 15:48:42 15:48:47

And I can -- I just described this here in the section and elsewhere. We can go to the words that I use, but they're co- -- well, they're administered in combination. Let's make sure we're clear with those words. 15:48:51 15:48:52 15:48:55 15:48:59 15:49:02

BY MR. KANE: 15:49:04

Q. Right. And we looked at what "in combination" means earlier. It's defined in the document, right? We looked at Paragraph 88, I want to say, of Vitti. 15:49:04 15:49:08 15:49:14 15:49:18

A. Yes. 15:49:33

Q. That second sentence? 15:49:34

A. Oh, yes, we looked at that. 15:49:37

Q. The expression "in combination with" means the VEGF antagonist is administered before, after, or concurrent with the pharmaceutical composition comprising the anti-Ang-2 antibody, right? 15:49:38 15:49:40 15:49:44 15:49:48 15:49:51

A. Yes. And I guess we didn't cover this before, but it -- the paragraph goes on to discuss what "before" and "after" mean, and it's clear that it's, again, in combination with. They're in combination with each other. 15:50:01 15:50:04 15:50:07 15:50:12 15:50:17

Q. The patient is receiving both therapeutic products or both therapeutics at some point in time during the therapy? 15:50:23 15:50:27 15:50:29

MS. KAYALI: Objection. Vague. Foundation. 15:50:37 15:50:38

A. I think I would say it a little different. I think that Vitti contemplates different therapies, but therapies that involve both the anti-Ang-2 and the VEGF inhibitor. 15:50:46 15:50:49 15:50:57 15:50:59 15:51:07

BY MR. KANE: 15:51:08

Q. Okay. But you -- 15:51:08

A. So together. 15:51:09

Q. But you would agree that the anti-VEGF and the Ang-2 inhibitor can be delivered via different routes of administration? 15:51:11 15:51:16 15:51:20

MS. KAYALI: Objection. Vague. 15:51:24

A. (Witness reviews document.) 15:51:46

I was going back to that paragraph. You may remember the number. I can find it. 15:51:47 15:51:50

BY MR. KANE: 15:51:53

Q. Paragraph 18. 15:51:53

A. That's what I thought. Here we go. 15:51:54

If what you mean is, as we discussed in Paragraph 18, as it says, "In certain embodiments, the Ang-2 inhibitor" -- I'm paraphrasing, but it's administered 15:52:02 15:52:04 15:52:08 15:52:13

intravenously or subcutaneously, and it says that the VEGF antagonist is administered intravitreally. 15:52:18 15:52:20 15:52:23

And I agree, those are two different routes. The point is that they're still combination, in combination with. 15:52:26 15:52:27 15:52:31

Q. Agreed, but I'm just focusing -- well, okay. 15:52:35 15:52:39

So then let's look at Paragraph 94. 15:52:55

MS. KAYALI: Paragraph 94 of Vitti? 15:53:01 15:53:01

MR. KANE: Yes. Thank you. 15:53:02

A. Okay, I'm there. 15:53:09

BY MR. KANE: 15:53:15

Q. And the first sentence says, "In certain embodiments, the pharmaceutical formulations are liquid formulations that may contain plus or minus 5" -- excuse me -- "may contain 5 plus or minus .75 mg per mL to 100 plus or minus 15 mg per mL of a VEGF antagonist." 15:53:15 15:53:16 15:53:18 15:53:21 15:53:27 15:53:34 15:53:39

Do you see that? 15:53:43

A. Yes. And I discuss this extensively in my report. 15:53:43 15:53:47

Q. Okay. And you would agree with me that aflibercept is a VEGF antagonist? 15:53:49 15:53:49

A. Yes. 15:53:58

Q. Okay. The next sentence says, "For example, the formulations of the present invention may comprise about 5 mg per mL; about 10 mg per mL; about 15 mg per mL; about 20 mg per mL; about 25 mg per mL; about 30 mg per mL; about 35 mg per mL; about 40 mg per mL; about 50 mg per mL; about 60 mg per mL; about 70 mg per mL; about 80 mg per mL; about 90 mg per mL; or about 100 mg per mL of a VEGF antagonist such as aflibercept," correct? 15:54:01 15:54:03 15:54:06 15:54:14 15:54:20 15:54:29 15:54:34 15:54:41 15:54:46 15:54:54

A. Yes, that's what's written. 15:55:01

Q. Okay. So in certain embodiments, Vitti teaches formulations of 100 mg per mL of aflibercept; do you agree? 15:55:05 15:55:07 15:55:20

MS. KAYALI: Objection. Vague. 15:55:28 15:55:29

A. (Witness reviews document.) 15:56:12

Well, I would -- I addressed exactly this point in -- sorry, well, Paragraph 102, page 59 of my declaration. I'm pretty sure this is one of the paragraphs referred to. 15:56:33 15:56:37 15:56:43 15:56:50

I believe, however, I'm referring to Dr. Falconer's report, so we can confirm, but I say, "Dr. Falconer identifies two purported disclosures in Vitti of formulations with a VEGF antagonist protein at or above 100 milligrams per milliliter." 15:56:53 15:56:56 15:57:00 15:57:03 15:57:07 15:57:10

And I say, "Both are part of a broad range that provides no disclosure of a high concentration of aflibercept formulation suitable for intravitreal injection," and then I talk about other aspects. 15:57:13 15:57:14 15:57:16 15:57:20 15:57:23

So that would be -- and then I continue to explain how the skilled person would understand these disclosures in Vitti. 15:57:26 15:57:29 15:57:31

BY MR. KANE: 15:57:35

Q. Okay. Did you -- let's look at Paragraph 107. 15:57:35 15:57:37

A. Of... 15:57:39

Q. Of the -- 15:57:40
A. Of Vitti or me? 15:57:42
Q. Vitti. 15:57:44
A. Okay. Okay, I'm at 107. 15:57:46
Q. Right. You see here it's describing, 15:57:58
"Exemplary formulations comprising a VEGF 15:58:03
antagonist can be used in context of the 15:58:06
present invention" -- let me read it over. 15:58:08
"Exemplary formulations comprising a 15:58:14
VEGF antagonist that can be used in the 15:58:16
context of the present invention are disclosed 15:58:18
in, e.g., in U.S. Patent numbers 7,531,173 and 15:58:21
7,608,261." 15:58:31
Do you see that? 15:58:40
A. Yes. And I may have misheard you. I 15:58:40
think you may have added an "in" before the 15:58:43
"e.g."; whereas, there's only an "in" after 15:58:46
the "e.g." 15:58:51
But anyway, just to clarify, I see it 15:58:52
with that caveat. 15:58:54
Q. Okay. And the '261 patent is Furfine 15:58:58
that we talked about earlier. Do you see 15:59:05

that? 15:59:08

A. Yeah. I mean, I see the number there. 15:59:20

I think I discussed this in my report, but we 15:59:22

can go to that if you want to -- 15:59:26

Q. Okay. And as we discussed earlier, 15:59:27

Claim 1 of Furfine claims an ophthalmic 15:59:31

formulation of 100 mg per mL of aflibercept 15:59:35

with certain excipients, right? 15:59:41

MS. KAYALI: Objection. 15:59:47

Foundation. 15:59:48

A. Claim 1 claims 1 to 100 mgs per mL of 15:59:55

aflibercept in this formulation. 16:00:01

BY MR. KANE: 16:00:04

Q. Okay. And so Vitti is pointing to 16:00:04

that and saying Furfine's 100 mg per mL 16:00:06

formulations can be used in this application, 16:00:13

correct? 16:00:20

MS. KAYALI: Objection. 16:00:23

Foundation. Mischaracterizes the record. 16:00:24

A. I mean, I -- as you know, I discuss 16:01:42

this over multiple paragraphs in my -- and 16:01:46

pages in my report. 16:01:51

Again, as we -- I agree that the second patent that you read in Paragraph 107 of Vitti is Furfine, and I agree that Furfine discloses formulations 1 to 100, including 100, I think that was your question, mgs per mL. 16:01:56 16:02:02 16:02:08 16:02:14 16:02:18 16:02:22

Q. Correct. So a person of ordinary skill reading Vitti would then understand that you could use Furfine's 100 mg per mL formulation in his invention? 16:02:22 16:02:26 16:02:29 16:02:32

MS. KAYALI: Objection. Vague. 16:02:43

A. (Witness reviews document.) 16:02:43

I mean, again, I discuss this extensively in Subsection 2, starting on page 59, and I go through -- it's all about the 100 mgs per mL with a focus on Vitti. That's what the first line of Paragraph 102 refers to, and throughout. 16:03:18 16:03:21 16:03:28 16:03:37 16:03:44 16:03:52

And I -- I don't think what you said is a fair characterization, unless you include what I say, which is the prior -- beginning of 103, for example, the prior art teaching away 16:03:56 16:03:59 16:04:03 16:04:07

from using a VEGF receptor fusion protein concentration of 100 mgs per mL in an intravitreal formulation, and the rest of what I include here. 16:04:11 16:04:15 16:04:18 16:04:21

I think it's important to read all the -- well, read Vitti as a whole and understand what Vitti is about, as I summarized in the summary section, and then throughout this analysis specifically about 100 milligrams per milliliter. 16:04:24 16:04:27 16:04:31 16:04:34 16:04:36 16:04:39

Q. Right. But you do agree with me that Vitti identifies Furfine's 100 mg per milliliter formulation as one of the formulations that can be used in the context of the present -- of his present invention, correct? 16:04:42 16:04:47 16:04:55 16:05:01 16:05:03 16:05:08

MS. KAYALI: Objection. Lacks foundation. 16:05:09 16:05:09

A. I agree that in Paragraph 107 of Vitti, the Vitti reference refers to exemplary formulations from two patents, one of which is the Furfine reference. It talks about 16:05:25 16:05:29 16:05:38 16:05:44

exemplary formulations, which I'm reading to be examples, and I think it's referring to the examples from the two -- sorry, from the Furfine, which ends in '261. 16:05:49 16:05:54 16:05:58 16:06:02

That's -- and then again I discuss the 100 mgs per mL throughout. Again, I agree, the Furfine certainly discusses 100 mgs per mL formulation, but not in -- not explicitly in the examples. 16:06:05 16:06:07 16:06:14 16:06:20 16:06:23

BY MR. KANE: 16:06:25

Q. Okay. Let's go back to Paragraph 94 again of Vitti. 16:06:25 16:06:27

A. Okay. I'm there. 16:06:36

Q. And this is Vitti talking about certain embodiments in his invention, correct? 16:06:39 16:06:44

A. It starts out with certain embodiments. 16:06:52 16:06:54

Q. And then it says, the last phrase at the -- well, at the end of Paragraph 94, "100 mgs per mL of a VEGF antagonist such as aflibercept," right? 16:06:56 16:06:59 16:07:03 16:07:05

A. Right. It says "about," but yes, it 16:07:14

says, "100 mgs per mL of a VEGF antagonist such as aflibercept." 16:07:16 16:07:18

Q. So isn't Vitti there consistent with his reference to Furfine's 100 mgs per mL formulations, likewise, stating explicitly that his invention contemplates using 100 mgs per mL formulations -- about 100 mgs per mL formulations of a VEGF antagonist such as aflibercept? 16:07:23 16:07:24 16:07:28 16:07:31 16:07:35 16:07:39 16:07:41

MS. KAYALI: Objection. Foundation. Compound. 16:07:46 16:07:53

A. I agree. I mean, that's there. I think there's no dispute about that last -- I guess it's a phrase after the semicolon in Paragraph 94 of Vitti. And I -- I mean, I developed my opinions which -- on exactly this subject, which go over multiple pages with that in mind. 16:08:02 16:08:06 16:08:11 16:08:15 16:08:20 16:08:23 16:08:25

I mean, we can go through them, but I would -- I would reference my -- the full set of opinions that I have on that here. 16:08:28 16:08:32 16:08:34

BY MR. KANE: 16:08:38

Q. So are we in agreement that Vitti teaches 100 mgs per mL of aflibercept for use in his invention? 16:08:38 16:08:40 16:08:47

A. I agree that Vitti states, as we've read, we don't need to read it again, the 100 mgs per mL of aflibercept. But I -- but I discuss reasons why I think Vitti -- well, that -- how the skilled person, I should say, would understand Vitti. For example, at the beginning of my Paragraph 103, "The prior art taught away from using a VEGF receptor -- the prior art taught away from using a VEGF receptor fusion protein concentration of 100 mgs per mL in an intravitreal formulation." 16:09:11 16:09:16 16:09:19 16:09:25 16:09:35 16:09:37 16:09:41 16:09:45 16:09:53 16:09:55 16:10:00

And I mean, I describe all this. So I want to -- I mean, all this is part of the analysis of the 100 mgs per mL. 16:10:02 16:10:07 16:10:09

Q. So but Vitti's prior art, too, right? 16:10:14 16:10:19

A. Vitti -- Vitti is a prior art to the '036 patent. 16:10:21 16:10:24

Q. Right. 16:10:26

A. Yes.
Q. And -- and Furfine is prior art to the '036 patent, correct?
A. Yes.
Q. And they both teach using 100 mg per mL intravitreal injection of aflibercept, right?
A. I agree that they both discuss the 100 mgs per mL of aflibercept. The difference to me as the skilled person is that Vitti is focusing on these combinations with the anti-Ang-2, and Furfine is focusing on aflibercept. And so that's -- that's why I'm differentiating the two.
I think the skilled person reading the Vitti would think about it as the combination. And actually, there are individual formulations of the anti-Ang-2. So that's a focus of Vitti. So they're different in that regard.
Q. Let's kind of take that -- so you agree that Furfine teaches 100 mgs per mL

intravitreal injection of aflibercept? 16:11:54

A. Yes, we've discussed that, yes. And I would refer to my previous comments, but we can go back to summarize, yes, Furfine does teach that. 16:12:01 16:12:04 16:12:07 16:12:10

Q. And would you agree that Vitti also teaches that? 16:12:16 16:12:17

MS. KAYALI: Objection. Vague. 16:12:20

A. I think Vitti is different, and I agree it discusses -- we've talked about Paragraph 94. I've analyzed this quite a bit. I don't know if I -- I don't think I would go so far as to say that Vitti teaches, because -- teaches the 100 mgs per mL, because when I read Vitti with the eyes of a skilled person in 2018, I read this as teaching combinations. 16:12:25 16:12:27 16:12:31 16:12:35 16:12:38 16:12:42 16:12:45 16:12:49 16:12:56

That's what the focus is on, teaching combinations of the anti-Ang-2 with the VEGF, like aflibercept, definitely. 16:12:57 16:13:00 16:13:08

BY MR. KANE: 16:13:10

Q. Right. 16:13:10

A. So I don't see the disclosures as the same in the two, and I don't see the interpretation of the skilled person the same in the two. This is exactly what I discuss in my declaration. 16:13:11 16:13:13 16:13:17 16:13:19 16:13:23

Q. Why can't the VEGF and Vitti be delivered at 100 mgs per mL formulation? 16:13:24 16:13:28

MS. KAYALI: Objection. Foundation. Vague. 16:13:37 16:13:37

A. Because, just what I've been saying, in Paragraph 62 -- I'm going to go to that and then back to 103 -- a skilled person would understand, the second sentence, "Vitti is primarily directed to methods and pharmaceutical formulations for treating vascular eye diseases using combinations," as we've been discussing, and then I won't read it explicitly, "of the anti-Ang-2 and VEGF antagonist like aflibercept." 16:13:37 16:14:19 16:14:23 16:14:27 16:14:30 16:14:33 16:14:35 16:14:38 16:14:42 16:14:51

It's the combinations that's the focus. Then the examples are to the 40 mgs per mL of aflibercept and then in combination 16:14:53 16:14:54 16:14:58

with an anti-Ang-2. And I -- then I discuss how the skilled person would understand Vitti with respect to the 100 mgs per mL disclosure, I mean, over many pages. 16:15:02 16:15:09 16:15:14 16:15:17

For example, Paragraph 103, "The prior art taught away from using VEGF receptor fusion protein concentration of 100 mgs per mL in an intravitreal formulation." 16:15:20 16:15:23 16:15:27 16:15:28

And I -- I mean, that's just one sentence I'm referring to, but I have a full analysis of Vitti. It's a very -- a skilled person would understand the teachings very differently than those of Furfine for the -- for these reasons I've summarized. 16:15:33 16:15:35 16:15:37 16:15:41 16:15:43 16:15:46

BY MR. KANE: 16:15:48

Q. Let's look at -- let's go to Paragraph 12 of Vitti. 16:15:48 16:15:50

A. Okay. 16:16:09

Q. And if you look in this paragraph, it says, "In the related aspect" -- "In a related aspect, the present invention provides methods for suppressing vascular leaks in the subject 16:16:10 16:16:16 16:16:22 16:16:24

with eye disease or disorder associated with angiogenesis, wherein the methods comprised administering a single dose of a VEGF antagonist followed by one or more doses of a pharmaceutical composition comprising an Ang-2 inhibitor to the subject in need thereof." 16:16:26 16:16:30 16:16:34 16:16:38 16:16:42 16:16:45

Do you see that? 16:16:51

A. Yes. 16:16:51

Q. Why couldn't that single dose be delivered with 100 mgs per mL formulation? 16:16:57 16:16:59

MS. KAYALI: Objection. Foundation. 16:17:06 16:17:06

A. I mean, again, I have extensive analysis on this in Paragraph 103, that same first sentence, page 60, "The prior art taught away from using a VEGF receptor fusion protein concentration of 100 mgs per mL in intravitreal formulation." 16:17:30 16:17:33 16:17:38 16:17:43 16:17:46 16:17:49

So the skilled person is reading Vitti. Vitti refers to aflibercept, Eylea, and the skilled person thinks about Vitti as teaching combinations, including the 16:17:52 16:17:54 16:18:01 16:18:06

Paragraph 12 which you've read, with the anti-Ang-2. And so the skilled person reading Vitti sees, okay, there's Eylea at 40 mgs per mL. Can we use another therapeutic approach with the 40 mgs per mL Eylea and innovate with an anti-Ang-2 inhibitor in combination? 16:18:08 16:18:11 16:18:15 16:18:23 16:18:31 16:18:40

That's how I think the skilled person would understand this. That's what I discuss in my report. 16:18:44 16:18:45 16:18:48

BY MR. KANE: 16:18:49

Q. So -- 16:18:49

MS. KAYALI: Counsel, please allow the witness to finish. 16:18:50 16:18:51

MR. KANE: Okay. 16:18:53

A. And again -- and again, that's -- it's different from Furfine for those reasons that I've been saying. 16:18:54 16:18:58 16:19:00

BY MR. KANE: 16:19:02

Q. Why does -- why does Vitti talk about 100 mgs per mL of aflibercept? 16:19:02 16:19:05

MS. KAYALI: Objection. Calls for speculation. 16:19:19 16:19:20

A. I mean, again, we talk about -- I mean, we talked about Paragraph 94. I don't know why -- I'm not in Vitti's head. I don't know why Vitti writes "100 mgs per mL of VEGF antagonist such as aflibercept." I agree it's there. Black and white. I'm telling you how reading this carefully in the eyes of a skilled person, how I think the skilled person would understand Vitti and the teachings -- I know you like the word -- the teachings of Vitti. 16:19:27 16:19:29 16:19:35 16:19:40 16:19:44 16:19:47 16:19:51 16:19:55 16:19:57 16:20:02 16:20:03

BY MR. KANE: 16:20:04

Q. So your understanding of the teachings of Vitti is use 40 mgs per mL of aflibercept with Ang-2? 16:20:04 16:20:05 16:20:09

MS. KAYALI: Objection. Foundation. Mischaracterizes the testimony. 16:20:12 16:20:15

You can answer. 16:20:21

A. No. I -- I think that's not a fair summary. Again, the -- all of the examples had 40 mgs per mL. I agree, there are other statements. But as I say, I mean, we can go 16:20:21 16:20:25 16:20:33 16:20:38

to other parts of my declaration if you want. 16:20:41

Paragraph 103, "The prior art taught 16:20:44

away from using a VEGF receptor fusion protein 16:20:46

concentration of 100 mgs per mL in an 16:20:49

intravitreal formulation." 16:20:54

And as I've summarized, we've gone to 16:20:56

this before, this Paragraph 62, I think the 16:20:59

skilled person reading Vitti would read about 16:21:07

a formulation strategy for using in 16:21:09

combination aflibercept and the anti-Ang-2. 16:21:13

I mean, that's -- like, the high level, that's 16:21:19

the teaching, and that's the reading, and 16:21:21

that's -- so I think it's a different -- it's 16:21:24

different from Furfine in that sense, so I'm 16:21:27

trying to explain. 16:21:31

BY MR. KANE: 16:21:38

Q. Remember, we -- turn to paragraph 127 16:21:38

of Vitti, please. 16:21:40

MS. KAYALI: You just dropped 16:21:43

off there. Paragraph what? 16:21:44

MR. KANE: Paragraph 127. 16:21:46

MS. KAYALI: Thank you. Of 16:21:47

Vitti? 16:21:47

MR. KANE: Yes. 16:21:48

BY MR. KANE: 16:21:56

Q. Again, we looked at this earlier. 16:21:56

It's the second sentence. 16:21:58

A. Yes. 16:21:59

Q. And here Vitti says, "From 10 mgs per 16:21:59

mL to 100 mgs per mL of aflibercept is 16:22:06

comprised -- is comprised in a prefilled 16:22:11

syringe and is administered intravitreally in 16:22:16

a volume of approximately 100 microliters," 16:22:19

right? 16:22:25

A. Yeah, it says "approximately up to," 16:22:25

right, but yeah, just to be explicit. 16:22:28

Q. So does that not -- is Vitti not 16:22:30

teaching there to use up to 100 mgs per mL of 16:22:33

aflibercept in a prefilled syringe 16:22:39

intravitreally? 16:22:42

MS. KAYALI: Objection. Asked 16:22:46

and answered. 16:22:47

A. (Witness reviews document.) 16:22:59

Okay. So now that I found where I 16:23:57

explicitly discuss Paragraph 127, again, I think this whole analysis of Vitti is important, but just to focus on paragraph -- well, Paragraph 120 of my report now, page 71, and referring to exactly that sentence that you read at the bottom of page 71, and then I state, "Both of these disclosures are of a very broad concentration range." 16:24:01 16:24:05 16:24:08 16:24:15 16:24:29 16:24:33 16:24:39 16:24:44

Then, again, I'm responding to Dr. Falconer, so I'm discussing Dr. Falconer. And then I'm maybe going to 121. I mean, everything that I say is here. I don't have to reread it. 16:24:47 16:24:50 16:24:57 16:25:01 16:25:04

Well, "A POSA reading Vitti would not understand formulations containing a VEGF antagonist at the top end" and then in quotes 'this range,'" but more importantly, "aflibercept at the top end of the 10 mg per mL to 100 mg per mL concentration range to be stable." 16:25:11 16:25:16 16:25:19 16:25:22 16:25:27 16:25:30 16:25:34

And I've explained in previous questions the context and the reasons. I can 16:25:36 16:25:41

go through more, if you want, but it's in my declaration. 16:25:42 16:25:45

BY MR. KANE: 16:25:46

Q. I'll ask you this then, Doctor, you already established Furfine teaches stable intravitreal formulation suitable -- stable -- aflibercept formulations suitable for intravitreal administration up to 100 mgs per mL, right? 16:25:46 16:25:52 16:26:00 16:26:04 16:26:07 16:26:11

MS. KAYALI: Objection. Foundation. 16:26:28 16:26:28

A. Again, I think if you're referring to column -- you said Furfine, I think. 16:26:35 16:26:37

BY MR. KANE: 16:26:40

Q. Furfine. 16:26:40

A. Yes. Thank you. 16:26:40

If you're referring to Column 2, starting at line 4, I agree Furfine says -- could say teaches in one aspect, "a stable liquid ophthalmic formulation is provided that comprises 1 to 100 mgs VEGF specific fusion protein antagonist," and then it talks about 16:26:45 16:26:45 16:26:53 16:26:56 16:26:59 16:27:05

various, you know, formulation components in the pH. 16:27:09 16:27:13

So I -- I agree. Furfine is a document that explicitly discusses -- well, the focus is on aflibercept as aflibercept, as opposed to Vitti, which we've been discussing and for the reasons I've been mentioning, I can go back to, I think -- I think the skilled person would understand the teachings differently of the two references. 16:27:15 16:27:22 16:27:26 16:27:32 16:27:35 16:27:38 16:27:43 16:27:45

Q. But Vitti, as we saw earlier, specifically says you can use the formulations of Furfine. 16:27:47 16:27:50 16:27:52

MS. KAYALI: Objection. 16:27:57

BY MR. KANE: 16:27:57

Q. Paragraph 107. 16:27:57

MS. KAYALI: Asked and answered. Mischaracterizes the record. 16:27:59 16:28:05

A. I don't think that's correct. Again, if you go to Paragraph 107, it specifically says "exemplary formulations." And then it refers to "e.g. in" and then two U.S. patents, 16:28:11 16:28:14 16:28:19 16:28:23

including Furfine. 16:28:30

So it says "exemplary," so I'm reading 16:28:33

that as the examples in Furfine. That's 16:28:36

what -- that's what "exemplary" means. It's 16:28:40

talking about exemplary formulations. Again, 16:28:44

that's not the only disclosure. There's 16:28:48

mention of Eylea throughout in the 40 mgs per 16:28:54

mL formulation, and that's -- again, I discuss 16:28:59

this in my declaration. 16:29:02

But that's the reason I think the 16:29:04

skilled person would understand Vitti 16:29:05

differently from Furfine. 16:29:09

BY MR. KANE: 16:29:13

Q. Turning back to Furfine, we were just 16:29:13

looking at the Column 2, starting at line 4 of 16:29:14

that paragraph. 16:29:20

A. Line 4? 16:29:24

Q. Yes. 16:29:25

A. Yes. Yes, I'm there. 16:29:27

Q. Isn't that an exemplary formulation? 16:29:28

MS. KAYALI: Objection. Vague. 16:29:43

A. It talks about embodiments. It's an 16:29:45

embodiment. Again, 107 says "exemplary formulations," and they're explicitly in Furfine examples. 16:29:53 16:30:00 16:30:02

So I think -- again, it's not just 107 of Vitti by itself. It's within the context of Vitti as a whole, which we've been discussing, the combination being the focus and the variations in the examples of Vitti being variations in the anti-Ang-2. 16:30:03 16:30:07 16:30:13 16:30:15 16:30:18 16:30:21

BY MR. KANE: 16:30:25

Q. What protein concentrations of aflibercept are taught by Vitti to be used in his invention? 16:30:25 16:30:31 16:30:40

MS. KAYALI: Objection. Vague. 16:30:50

A. Again, I summarize in Paragraph 62 of my declaration, page 31, the exemplary formulations contain 40 mgs per mL of aflibercept in combination with this anti-Ang. So that's taught. 16:31:10 16:31:16 16:31:24 16:31:27 16:31:29

I agree that it discusses in the various places, I mean, they talk about 100 mgs per mL. But I explicitly say in 16:31:34 16:31:38 16:31:45

Paragraph 103, page 60, the very top, "The prior art taught away from using a VEGF receptor fusion protein concentration of 100 mgs per mL in intravitreal formulation." 16:31:51 16:31:56 16:31:59 16:32:00

Then I discuss how the skilled person would understand Vitti in that context and why, given the overall disclosures in Vitti. 16:32:06 16:32:08 16:32:14

MS. KAYALI: Can I ask for a -- just a time check? I think we've got maybe like a minute left. 16:32:20 16:32:21 16:32:23

THE VIDEOGRAPHER: Right now we're at seven hours. 16:32:26 16:32:26

MS. KAYALI: Great. Okay. Well, then should we go off the record, and we'll take just a couple of minutes and hopefully get everyone out of here quickly. 16:32:27 16:32:32 16:32:35 16:32:38

THE VIDEOGRAPHER: This is the end of Media No. 5. We are going off the record. The time is 4:33 p.m. 16:32:45 16:32:47 16:32:48

16:49:58

(Recess taken from 4:33 p.m. to 4:50 p.m.) 16:49:58 16:49:58

THE VIDEOGRAPHER: This is the beginning of Media No. 6. We are going back on the record. The time is 4:50 p.m. 16:49:58 16:50:03 16:50:03 16:50:07

MS. KAYALI: Thank you, Dr. Trout. 16:50:10 16:50:10

Patent owners have no questions for you today. 16:50:12 16:50:13

THE WITNESS: Okay. Thank you. 16:50:14

THE VIDEOGRAPHER: This is the end of Media No. 6. This marks the end of today's deposition of Dr. Bernhardt Trout. We are going off the record. The time is 4:51 p.m. 16:50:16 16:50:16 16:50:18 16:50:21 16:50:23

THE STENOGRAPHER: Do you need a rough draft? 16:50:24 16:50:24

MS. KAYALI: Yes, please. And we will take it as soon as you've got it. 16:50:37 16:50:37

What would normal be for the final? 16:50:37 16:50:37

THE STENOGRAPHER: Normal is two weeks. 16:50:37 16:50:37

MS. KAYALI: What would it ruin your life? 16:50:37

THE STENOGRAPHER: Just tell me when you need it and I'll be sure you get it. 16:50:37

MS. KAYALI: How about like next Tuesday morning. 16:50:37

THE STENOGRAPHER: Mr. Chen, you need a rough, is that right? 16:50:37

MR. CHEN: Yes, we'll take a rough. 16:51:43

THE STENOGRAPHER: Did you want your final expedited as well? 16:51:47

MR. CHEN: Yes, please. 16:51:47

THE STENOGRAPHER: Thank you. 16:51:47

(Deposition concluded at 4:51 p.m.) 16:51:50

CERTIFICATE OF SHORTHAND REPORTER-NOTARY PUBLIC

I, DARLENE M. COPPOLA, Certified Reporter and Notary Public within and for the state of Massachussetts do hereby certify:

That Bernhardt L. Trout, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

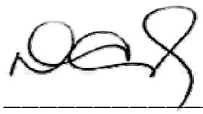
I further certify that the adverse party, Regeneron Pharmaceuticals, Inc., was represented by counsel at the deposition.

I further certify that the deposition of Bernhardt L. Trout, Ph.D., occurred at the offices of Dechert LLP at One International Place 100 Oliver Street 40th Floor, Boston, MA on Thursday, August 27th, 2026, commencing at 8:10 a.m. to 4:33 p.m.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties to this action, and that I am in no way interested, financially or otherwise, in the outcome of this

matter.

WITNESS MY HAND THIS 31st day of August 2026.



_____

DARLENE M. COPPOLA My commission expires:

NOTARY PUBLIC November 2, 2029

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case PDR2025-00085

U.S.Patent 12,168,036

****

ALVOTECH USA INC. and ALVOTECH, INC.,

Petitioner

vs.

REGENERON PHARMACEUTICALS, INC.,

Patent Owner

****

I, BERNHARDT L. TROUT, PH.D., say that I have read the foregoing deposition and hereby declare under penalty of perjury the foregoing is true and correct: (as prepared) (as corrected on errata.)

Executed this _____ day of _____, 2026, at _____, _____.

_____

BERNHARDT L. TROUT, PH.D.

CORRECTION PAGE

DEPONENT: BERNHARDT L. TROUT, PH.D.

DATE TAKEN: AUGUST 27 2026

CASE: ALVOTECH USA INC.

VS. REGENERON PHARMACEUTICALS, INC.

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